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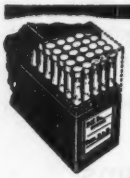

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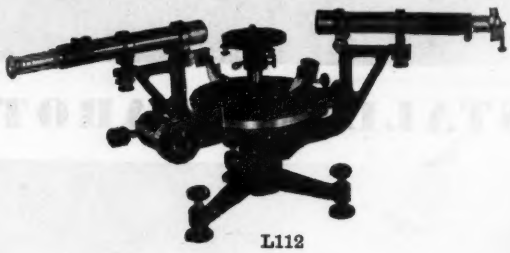

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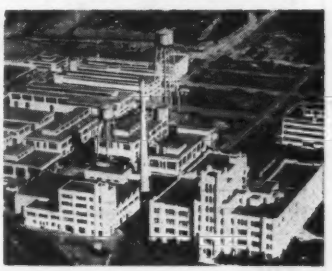

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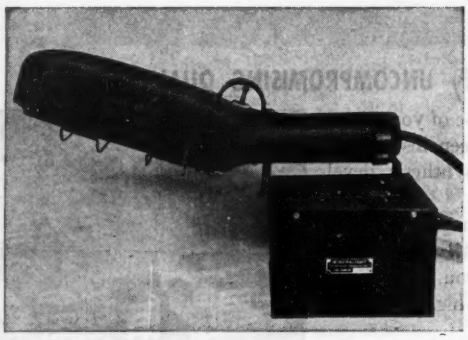

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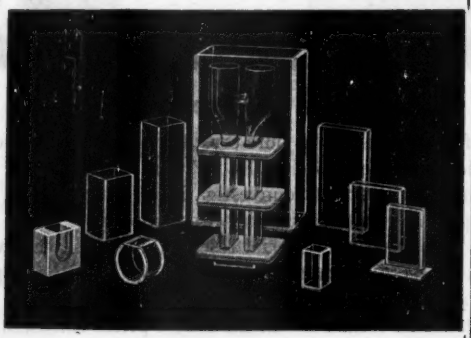

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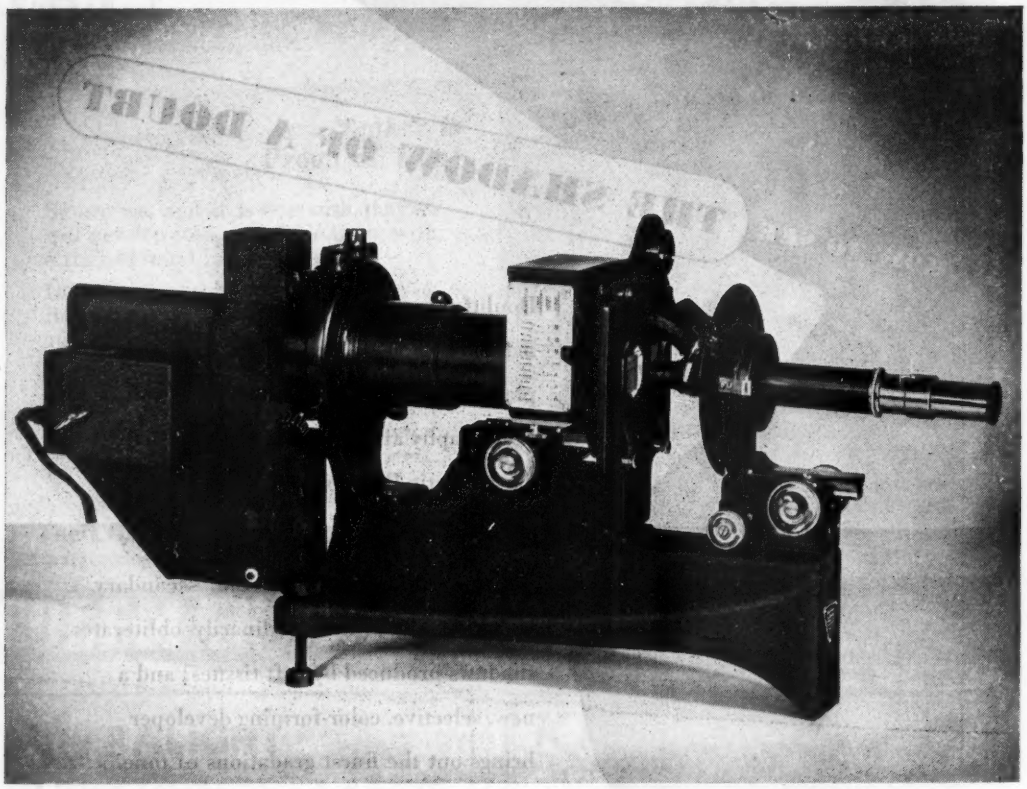

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SOME NEW ASPECTS OF THE RELATIONSHIP OF CHEMICAL STRUCTURE TO BIOLOGICAL ACTIVITY*

By Dr. D. W. WOOLLEY

LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH, NEW YORK, N. Y.

ALTHOUGH for many years it has been recognized that relationships exist between the chemical structures of certain compounds and their pharmacological properties, those interdependencies[1] which have been observed have served more to correlate existing data in many isolated sectors of the field of drug action than to serve as guideposts on the road of medicine and research ahead. Therefore it has seemed desirable to examine some of the facts recently uncovered in nutritional research in an effort to gain new vantage points from which to survey the field of the relationship of chemical structure to biological activity. From these vantage points it may be possible to see some of the roads along which future progress may be made.

Much of the material from which conclusions will be drawn in this paper had its origin in the observation of Woods,[2] who in 1940 reported that the bacteriostatic action of sulfanilamide was reversed competitively by *p*-aminobenzoic acid. These two antagonistic substances are very closely related structurally, since they differ only in the fact that the sulfonamide group of the former is replaced by a carboxyl group in the latter. The hypothesis was

* Received for publication October 27, 1944.

[1] Thus while many studies have been made of the relationship of such factors as the length of side chains to a given biological activity in a series of compounds, these studies have followed the original empirical discovery of an active member of the series.

[2] D. D. Woods, *Brit. Jour. Exp. Path.*, 21: 74, 1940.

advanced that the bacteriostatic action of the sulfonamides was to be explained by the competition of the drugs with *p*-aminobenzoic acid at some vital stage of metabolism in which *p*-aminobenzoic acid was concerned. This hypothesis grew in stature when it was shown that *p*-aminobenzoic acid was a cell constituent and that it was actually an indispensable nutrient or vitamin for several species.[3,4,5] Pursuing the hypothesis of Woods, other investigators, in efforts to produce bacteriostatic compounds, applied to other vitamins structural changes similar to those involved in passing from *p*-aminobenzoic acid to sulfanilamide. In this way McIlwain[6] found that pyridine-3-sulfonic acid inhibited bacterial growth in competition with nicotinic acid and that α-aminosulfonic acids acted similarly in competition with α-amino acids.[7] Likewise, Snell[8] and subsequently Kuhn *et al.*[9] and McIlwain[10] showed that thiopanic acid (pantoyltaurine, N-[α,γ-dihydroxy-β,β,-dimethylbutyryl]-taurine) inhibited bacterial growth in competition with pantothenic acid. In all of these instances it could be said that the sulfonic acids prevented growth by the production of specific deficiencies, since the action of the drugs was nullified by sufficient amounts of the vitamin or metabolite concerned.

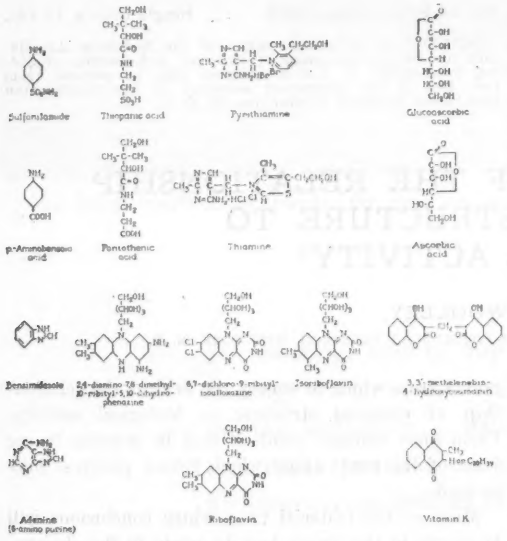


FIG. 1

Thus far, the work involved one type of structural change, and was limited by the desire to produce only inhibition of microbial growth. Although the techniques of bacteriology have been and will continue to be of first rate importance in this field, it must be remembered that bacteriostatic drugs form only a small part of the list of useful chemotherapeutic agents, and that the same principles used to produce bacteriostatic substances may serve to guide the search for useful drugs of other categories.

The next advance was made when it was shown that certain compounds related structurally to the vitamins or other metabolites produced typical signs of deficiency diseases in animals. The first clear recognition of this fact appeared when Woolley and White[11] showed that pyrithiamine caused the production of typical signs of thiamine deficiency in mice, and that the disease so produced was preventable or curable by sufficient amounts of thiamine. At about the same time Woolley and Krampitz[12] reported that glucoascorbic acid caused the production of a disease with most of the characteristic signs of scurvy.[13] In guinea pigs, this disease was preventable by ascorbic acid.[14] Some time before this Overman *et al.*[15] had shown that the signs of vitamin K deficiency which are produced by 3,3'-methylenebis(4-hydroxycoumarin) were prevented by vitamin K to which the coumarin has some structural similarity. Furthermore, Emerson and Tischler[16] have shown that isoriboflavin caused signs of riboflavin deficiency in rats which were reversed by adequate amounts of the vitamin. Woolley[17] reported that the structurally-related phenazine analog of riboflavin caused typical riboflavin deficiency in mice and that the disease was preventable by excess of the vitamin. Finally, the production of nicotinic acid deficiency in mice with β-acetylpyridine and its prevention with nicotinic acid has been observed recently.[18]

Interspersed with these observations on animals there has been a long series of illuminating results on the inhibition of microbial growth with analogs of various metabolites, and the reversal of this effect with increased amounts of the metabolite concerned.

[3] S. D. Rubbo and J. M. Gillespie, *Nature*, 146: 838, 1940.

[4] K. C. Blanchard, *Jour. Biol. Chem.*, 140: 919, 1941.

[5] L. A. Underkofler, A. C. Bantz and W. H. Peterson, *Jour. Bact.*, 45: 183, 1943.

[6] H. McIlwain, *Brit. Jour. Exp. Path.*, 21: 136, 1940.

[7] H. McIlwain, *Jour. Chem. Soc.*, page 75, 1941.

[8] E. E. Snell, *Jour. Biol. Chem.*, 139: 975, 1941.

[9] R. Kuhn, T. Wieland and E. T. Möller, *Ber. deutsch. chem. Ges.*, 74: 1605, 1941.

[10] H. McIlwain, *Biochem. Jour.*, 36: 417, 1942.

[11] D. W. Woolley and A. G. C. White, *Jour. Biol. Chem.*, 149: 285, 1943.

[12] D. W. Woolley and L. O. Krampitz, *Jour. Exper. Med.*, 78: 333, 1943.

[13] This and subsequent studies have provided valuable clues to the mode of action of some of the vitamins or metabolites. The use of inhibitory analogs for the investigation of the mode of action of the vitamins, on the one hand, and of certain drugs on the other, is an inviting approach, but a discussion of this branch of the subject can not be included here.

[14] D. W. Woolley, *Fed. Proc.*, 3: 97, 1944.

[15] R. S. Overman, J. B. Field, C. A. Baumann and K. P. Link, *Jour. Nutrition*, 23: 589, 1942.

[16] G. A. Emerson and M. Tishler, *Proc. Soc. Exper. Biol. and Med.*, 55: 184, 1944.

[17] D. W. Woolley, *Jour. Biol. Chem.*, 154: 31, 1944.

[18] D. W. Woolley, *J. Biol. Chem.*, in press.

An exhaustive review would not be in order here, but the action of pyrithiamine reversed by thiamine,[19] of benzimidazole reversed by adenine or guanine,[20] of 6,7-dichloro-9-ribitylisoalloxazine reversed by riboflavin,[21] of iodinin reversed by vitamin K,[22] and of desthiobiotin reversed by biotin[23,24] may be noted.

With this cursory scanning of the field, let us look about for vantage points from which the roads ahead may be discerned. In particular, let us examine what new aspects of the relationship of chemical structure to biological activity may have become apparent.

The first aspect is the formation of new types of drugs the action of which may, in part, be predicted. The knowledge of the specific histological and biochemical signs produced by deficiencies of the various vitamins and hormones is being steadily increased. It has already been seen that it is possible to synthesize structural analogs of several vitamins which produce in animals the characteristic signs of deficiency of the vitamins to which the analogs are related. Thus it has been possible to produce pharmacological manifestations similar to the signs of specific vitamin deficiencies by administering suitable analogs of the vitamins. Some of the changes which these analogs or drugs elicit could be predicted at least in part, since the signs of the deficiencies have been established. Such drugs carry with them the rather unique advantage that their antidotes, that is, their related vitamins, usually are known prior to the trial of the compound.

The agents thus far produced as vitamin analogs have caused various specific pharmacological signs, but the latter have not indicated a clinical use of the substances. It is not inconceivable, however, that certain specific changes which are brought about by a given vitamin deficiency may be effective and desirable therapeutically. The study of an inhibitory analog of the vitamin in question would then be of interest. In retrospect it can be seen that the drug, 3,3′-methylenebis(4-hydroxycoumarin), which causes signs similar to those seen in vitamin K deficiency, is related structurally to this vitamin. Furthermore, the action of the drug can be reversed by the vitamin. This drug was not conceived on the basis of its relationship to vitamin K—but with the backward glance at this case to fortify us, it may be possible in the future to proceed in a less circuitous manner than was necessary for the development of this coumarin derivative. At the present time, that which has been done is the prediction and subsequent synthesis of compounds which bring about at least some anticipated pharmacological signs; that which remains to be done is the production of types of compounds having useful therapeutic action.

There are diseases known which are due to the overproduction, or to the diminished rate of destruction, of some of the hormones. It would be of interest to determine whether the administration of an inhibitory analog of the hormone concerned would effectively antagonize the extra amount of hormone, and thus combat the disease. It may be questioned whether it is possible to produce antagonistic analogs of the hormones. The results with glucoascorbic acid[12] suggest that it is possible to do this. Ascorbic acid may be regarded as a hormone in all species except guinea pigs and the primates, and it has been seen that glucoascorbic acid antagonizes the action of ascorbic acid in species for which ascorbic acid is not a dietary essential.

Until the present, attention in connection with inhibitory analogs has been focused largely on the production of chemotherapeutic agents useful in combating infections. The possible value of the vitamin analog approach to this problem has been indicated by the encouraging results of McIlwain and Hawking[25] with thiopanic acid (pantoyltaurine). It may be that not only new magic bullets against infection can be cast in this mold, but that, in addition, agents of use in other situations may be formed.

The second new aspect of the relation of chemical structure to biological activity is an outgrowth of the first. If it is possible to form specific drugs which bring about the same effects as are produced by deficiencies of vitamins or other metabolites, then it is of interest and importance to see what structural changes in the metabolite molecule will result in the production of such drugs. Thus far, two general methods of forming such compounds may be discerned. In addition, there is a third group of structural changes about which it is not as yet possible to make generalizations.

The first general method of modifying the structure of metabolites in order to produce inhibitory compounds involves the exchange of a carboxyl group of the metabolite for some other group. The most widely-studied exchange is that of a sulfonic acid or sulfonamide group for the carboxyl. Sulfanilamide and the related sulfonamides are familiar examples of this type of change in which the metabolite is *p*-aminobenzoic acid. Pyridine-3-sulfonic acid, the α-amino sulfonic acids, and thiopanic acid (pantoyltaurine) are examples of the application of this

[19] D. W. Woolley and A. G. C. White, *Jour. Exper. Med.*, 78: 489, 1943.
[20] D. W. Woolley, *Jour. Biol. Chem.*, 152: 225, 1944.
[21] R. Kuhn, F. Weygand and E. F. Möller, *Ber. deutsch. chem. Ges.*, 76: 1044, 1943.
[22] H. McIlwain, *Biochem. Jour.*, 37: 265, 1943.
[23] K. Dittmer, D. B. Melville and V. du Vigneaud, SCIENCE, 99: 203, 1944.
[24] V. G. Lilly and L. H. Leonian, SCIENCE, 99: 205, 1944.
[25] H. McIlwain and F. Hawking, *Lancet*, I: 449, 1943.

change to other metabolites. It is a matter of some mystery why analogs produced by use of this type of alteration are not able to bring about signs of deficiency diseases in animals,[26] while they are quite active in this respect in microbial species. The fact that several drugs which are active as therapeutic agents against infectious diseases come from this group (sulfonamides and pantoyltaurine) may be related to the relative immunity of animal organisms to such compounds. It is possible to achieve bacteriostatic concentrations of the drugs in the host without doing violence to the animal.

Inhibitory compounds may also be formed by replacing the carboxyl group with –CO–R. Auhagen[27] showed that such a change in *p*-aminobenzoic acid to yield *p*-amino-aceto-phenone resulted in a drug which would inhibit the growth of several bacteria competitively with *p*-aminobenzoic acid. A related ketone was chemotherapeutically active against certain bacterial infections of mice. Woolley[18] showed that 3-acetylpyridine produced nicotinic acid deficiency in animals and that phenyl pantothenone (N-[α, γ-dihydroxy-β,-β,-dimethylbutyryl]-1-amino-ethyl-phenyl ketone acted competitively with pantothenic acid. In contrast to the findings with the sulfonic acid derivatives mentioned above, acetylpyridine was not an effective inhibitor of the growth of bacteria.

The second general method of deriving inhibitory compounds involves the replacement of one or more atoms in the ring systems of cyclic metabolites. Since so many compounds of biological importance are cyclic in structure, this method of approach is particularly inviting, and has proved rather fruitful. The type of change which has been applied to the widest variety of metabolites is the substitution of C for N in six-membered rings. In this category are benzimidazole[20] related to the purines; 2,4-diamino-7,8-dimethyl-10-ribityl-5,10-dihydrophenazine[17] related to riboflavin; *o*-aminobenzylmethylthiazolium chloride[28] related to thiamine; and iodinin[22] related to certain naturally-occurring anthroquinones, and more remotely to vitamin K. Here, as in the case of the sulfonic acid or amide compounds, the method of structural change has apparently worked in every instance in which it has been tried. It will really be remarkable if this record continues to stand in the face of more varied application of the principle. Pyrithiamine,[11] the first inhibitory compound discovered to belong to this second general class of structural change, involves a slightly different type of alteration of a metabolite. In this substance –CH : CH– replaces the S atom of the thiazole ring of thiamine. Similarly, 3,3′-methylenebis(4-hydroxycoumarin) may be viewed as a structural analog of vitamin K in which one C atom in the ring system of the vitamin has been replaced by an O atom and changes have been made in the nuclear substituents. However, the relationship here is not as clear, both from a structural and a biological viewpoint, as in the case of several of the other examples cited.

As with the inhibitory compounds derived by the first general method of structural change, so with those arising from the second general method there are very many questions to which adequate answers can not yet be given. A few should be mentioned here. In the case of benzimidazole which is related structurally to, and whose antimicrobial action is reversed competitively by, adenine, the inhibitory compound differs from the metabolite not only in the ring system but also in the fact that benzimidazole lacks the $-NH_2$ group which is present as a substituent of the ring in adenine. It was thought that if benzimidazole were made more analogous to adenine by substituting an amino group in the proper position, a more active compound would result. Actually, however, this substitution did not increase the potency of the benzimidazole.[20] With the exception of pyrithiamine a similar problem concerning the nature of the proper nuclear substituents exists for all representatives of this second general class of compounds. From this it must be concluded that there are many things yet to learn about the relation of the side chains to biological activity in such substances. Another question is whether the production of inhibitory analogs by, let us say, the exchange of C atoms for N atoms is a unilaterally effective process, or whether it is equally effective to exchange N for C. Thus it appears that trading benzene rings for pyrimidine rings results in inhibitory compounds in all the cases tried. It would be well to know if the replacement of benzene rings in metabolites with pyridine or pyrimidine rings likewise would be effective. From the competitive action of aminonicotinic acid with *p*-aminobenzoic acid[29] it would seem that the process is not unilateral, but more data are required before a conclusion can be reached on this point. With a subject in its infancy as this entire one is, there are sure to be many more questions than answers, and the few answers that are available are more in the nature of hypotheses than of facts.

The third group of structural changes, *i.e.*, the miscellaneous types of alteration of metabolites which yield inhibitory compounds, need not be catalogued here since no guideposts to future research can yet be seen from it. In this group belong such substances as glucoascorbic acid,[12] α-methyl-pantothenic acid,[30] and desthiobiotin.[23] Some of these derivatives have

[26] D. W. Woolley and A. G. C. White, *Proc. Soc. Exper. Biol. and Med.*, 52: 106, 1943.

[27] E. Auhagen, *Zeit. f. physiol. Chem.*, 274: 48, 1942.

[28] R. R. Sealock and R. L. Goodland, *Jour. Am. Chem. Soc.*, 66: 507, 1944.

[29] O. H. Johnson, D. E. Green and Ruth Pauli, *Jour. Biol. Chem.*, 153: 37, 1944.

[30] M. A. Pollack, *Jour. Am. Chem. Soc.*, 65: 1335, 1943.

been of considerable value in the investigation of vitamin function, but this branch of the subject of inhibitory compounds and their uses does not concern us here.

It must not be inferred that it is only necessary to alter the structure of a metabolite in any way in order to produce an inhibitory derivative. Much testing of compounds related structurally to each of the several vitamins has shown that most of these derivatives are biologically inert and definitely not inhibitory in the systems in which they were tested.

On the other hand, there appears to be no unique manner in which the structure of a given metabolite must be altered in order to produce an inhibitory drug. For example, isoriboflavin,[16] 6,7-dichloro-9-ribityl isoalloxazine,[21] and 2,4-diamino-7,8-dimethyl-10-ribityl-5,10-dihydrophenazine,[17] three analogs of riboflavin in which the type of structural change is fundamentally different, all have been shown to produce riboflavin deficiency in various species. Also, Johnson *et al.*[29] have called attention to several ways in which the structure of *p*-aminobenzoic acid may be altered in order to produce bacteriostatic compounds.

Again it must be pointed out that the present work has been erected alongside of a new and dim trail to act as a guiding sign until the road has become a well-traveled highway, when a more substantial and pretentious marker may be raised. Furthermore, it must be stated that no attempt has been made to constrain the view with some of the hypotheses now prevalent which would picture the inhibitory metabolite analogs as competing at enzyme surfaces for the corresponding metabolites. Such hypotheses have served well as guides for further investigation, but at present seem to lack sufficient experimental support to make them more than speculations. The facts, however, must be kept clearly in view. These facts are that certain compounds related structurally to various biologically important substances cause specific signs of deficiency diseases, and that these signs are reversed by the metabolites in question when given in adequate amounts.

OBITUARY

WILLIAM WILLIAMS HENDERSON
1879–1944

FOLLOWING a confining illness of approximately two months resulting from heart trouble, Dr. W. W. Henderson, prominent and beloved teacher at the Utah State Agricultural College for twenty-one years, died on October 31, 1944.

He was born at Clarkston, Cache County, Utah, on May 23, 1879. When he was nine years of age, his parents moved the family to Robin, Idaho, where he was raised on a farm. His natural thirst for learning brought him to the Brigham Young College at Logan, and from this institution he obtained a bachelor of arts degree in June, 1903. Immediately following this, he entered the University of Chicago, later transferring to Cornell University, where he obtained a master of science degree in 1905.

Returning from Cornell University, W. W. Henderson became instructor in biology at the Brigham Young College, serving in this position from 1905 to 1910. From 1910 to 1914, he was principal of the Weber Academy in Ogden.

In 1917, Professor Henderson came to the Utah State Agricultural College as head of the department of zoology and entomology, professor of zoology and entomology and entomologist of the Agricultural Experiment Station. He continued in these positions until 1920, when he became president of the Brigham Young College, serving there until that institution was discontinued in 1926.

Obtaining his doctor of philosophy degree in 1924 from the University of California, Dr. Henderson returned to the Utah State Agricultural College in 1926, resuming his former position. With the exception of one year, 1928–29, when he was on leave of absence, he served the college continuously from 1926 until the time of his death.

Dr. Henderson took a prominent part in all campus activities of a scholastic or professional nature. For years he served as chairman of the attendance and scholarship committee. He aided in organizing and sponsoring such campus organizations as the Genetics Seminar, Zoology Seminar and the Utazoa Society. He rendered valuable service in establishing the Utah State Chapter of the Society of the Sigma Xi on the campus in 1942 and served as its president during 1943–44. He was a member of the Faculty Advisory Council and other faculty organizations and committees.

Dr. Henderson possessed a natural penchant for discovering truth and a zeal for teaching it. He searched for it in its original sources of the great out-of-doors, in the laboratory and in the works of other researchers. He was an earnest courageous champion of all truth and of the scientific method of obtaining it. However, because of the large amount of executive work required of him in most of his positions, he was prevented from doing as much original research as he desired to do. Nevertheless, he made important contributions to science, particularly with reference to the taxonomy of western Orthoptera.

His collection of Orthoptera numbers thousands of specimens and dozens of species that he has collected in the fields, in canyons, on mountains and on the deserts of Utah.

Dr. Henderson held membership in the following honorary and scientific societies: Sigma Xi, Cornell Chapter, 1905; Phi Kappa Phi; American Association for the Advancement of Science; Entomological Society of America; Pan Pacific Entomological Society; American Genetic Association; American Eugenic Society; American Association of University Professors; and Utah Academy of Sciences, Arts and Letters.

Dr. Henderson's greatest contribution was perhaps that which he made in the classroom. He was particularly efficient as a teacher. This resulted from a combination of factors, including his natural capabilities, proficient training, his continuous, thorough and systematic preparation and presentation of subject-matter, together with his sympathetic understanding of student character and problems. His nobleness of character, wisdom, meekness, sincerity, guilelessness, efficiency and friendliness developed in students and associates alike a wholesome respect and sincere affection.

The high esteem and kind affection in which the students of Utah State Agricultural College held this devoted teacher was manifest by their dedication of the 1935 *Buzzer* to him.

To all his work Dr. Henderson brought enthusiasm, freshness and excellence. He was tireless in all his efforts, and his enthusiasm, zeal and devotion to duty often carried him far beyond the point to which his physical strength should have been taxed.

The interests and work of Dr. Henderson extended beyond the college campus to community, state and national problems.

Dr. Henderson was highly respected and greatly admired by all who knew him. In his passing, the college, the community and the state of Utah have lost a great teacher, a valiant scientist, a sincere friend and a champion of truth.

CHARLES J. SORENSON

RECENT DEATHS

DR. CHARLES FELTON SCOTT, professor emeritus of electrical engineering of Yale University, a consulting engineer of the Westinghouse Electric and Manufacturing Company, died on December 17. He was eighty years old.

DR. ROSCOE CONKLING YOUNG, head of the department of physics at the College of William and Mary, died on November 22 at the age of fifty-nine years.

THE REVEREND FRANCIS W. POWER, professor of micro-analysis at Fordham University, died on December 15. He was fifty-one years old.

THE death is announced of Dr. Charles Anderson, who recently retired as director of the Australian Museum at Sidney. A correspondent writes: "He was primarily a geologist, but was a man of unusually wide interests and training. His services and kindnesses to visiting American scientists were unfailing and unforgetable by those who enjoyed them."

SCIENTIFIC EVENTS

GRANTS OF THE NUFFIELD FOUNDATION

IT is reported in *The Times*, London, that the trustees of the Nuffield Foundation, in order to carry out one of its primary objects, the advancement of health, particularly by the furtherance of teaching and research, have offered to the Universities of Durham, Glasgow and Manchester grants amounting to £150,000 to assist them in carrying out plans that they have submitted for the development of teaching and research in industrial health as soon as suitable staffs can be appointed.

These grants will be spread over a period of ten years. Manchester, where it is proposed to create a chair of industrial health, will receive £70,000. Durham has been offered £40,000 for the establishment of a department under a university reader. A similar amount is being allocated to Glasgow for a sub-department of industrial health within the existing department of social medicine.

The Minister of Labor and National Service, Mr. Bevin, has assured Sir William Goodenough (chairman of the trustees) of his warm approval of the proposal, which he regards as an important contribution to further progress in industrial health.

A statement issued by the foundation points out that the maintenance of a healthy industrial population involves the provision of greater facilities than now exist for education and research in problems of industrial health. Great Britain has no university department devoted to educational work in industrial health and no facilities for post-graduate training in industrial medicine.

THE NUTRITION FOUNDATION

THE third annual meeting of the Board of Trustees of the Nutrition Foundation, of which George A. Sloan is president, was held in Minneapolis on November 30. At this meeting grants for research of $127,750 were made.

Since its organization by food and related manufacturers three years ago, the foundation has made appropriations of $654,700 to support ninety-five sepa-

rate research projects in American universities. Fifty food and related manufacturers have contributed the sum of $1,524,500 to carry on its work.

Fourteen of the grants approved at the meeting are for the extension of studies which have been already started and which have yielded results that have made it seem wise to extend the work for from two to three years.

A luncheon meeting which immediately preceded the meeting of the Board of Trustees, attended by a number of distinguished representatives of education, science, industry, agriculture and finance, was addressed by Colonel Rohland A. Isker, in charge of Subsistence Research for the Army.

Grants approved at the meeting included renewals of the following fourteen studies now under way:

The synthesis and utilization of liver protein, Stanford University	1 yr.	$ 4,000
The quantitative study of the nutrients of cow's milk, Cornell University	1 yr.	1,500
Relation of niacin and other B-vitamin deficiencies to oral diseases, University of California	3 yrs.	12,000
Liver function in relation to certain carcinogenous agents, New York Memorial Hospital	3 yrs.	7,800
Metabolism of Vitamin A, Mount Sinai Hospital	1 yr.	3,300
Concentration of new vitamins, Rockefeller Institute	2 yrs.	6,800
Evaluating foodstuffs for meeting the human protein requirement, University of Rochester	1 yr.	3,000
Growth, reproduction and lactation in rats on highly purified diets, Fordham University	1 yr.	2,200
Micro-biological analysis of amino acids, University of California	3 yrs.	9,000
Absorption of iron compounds in anemia, Vanderbilt University	3 yrs.	7,500
Nutritive role of hydroxy fatty acids, Massachusetts Institute of Technology	2 yrs.	4,800
Carbohydrate metabolism, Columbia University	3 yrs.	15,000
Diet and congenital malformations, University of Cincinnati	3 yrs.	7,500
Pyruvate metabolism with special emphasis on the role of acetoin, Harvard University	3 yrs.	9,000

The new grants approved included:

Research in community nutrition, Harvard University	2 yrs.	5,600
The iron requirement of the adolescent girl, University of Chicago	1 yr.	1,800
The intermediary metabolism of carotene, University of Southern California	1 yr.	3,000
Nature of the ascending paralysis produced in dogs on a B-complex deficient diet and responding to biotin therapy, Duke University	1 yr.	1,500
Studies on pantothenic acid, Meharry Medical College	1 yr.	850

THE AMERICAN SOCIETY OF TROPICAL MEDICINE

THE forty-first annual meeting of the American Society of Tropical Medicine was held in St. Louis from November 13 to 16 with headquarters at the Statler Hotel. The meeting was held as usual during the annual meeting of the Southern Medical Association. Also as usual the society held a dinner meeting with the American Academy of Tropical Medicine and another session with the National Malaria Society.

Three scientific sessions were held. Thirty-five papers were listed on the program, of which eight were read by title. All sessions were well attended, more than a hundred and seventy-five members being present at some of the meetings. The society now has one thousand two hundred and thirteen members, as compared with nine hundred and fifty-two at this time last year.

Most of the opening scientific session was devoted to the general theme of war and post-war tropical medicine. Papers were presented by Dr. L. E. Napier, Major Douglass W. Walker, Lieutenant Colonel Phillip T. Knies, Dr. Henry E. Meleney and Major George W. Hunter, III. Major Hunter's paper concerned the activities of the Distributing Center for Parasitological Specimens during 1944, and attention was again called to the importance of this endeavor and the urgent need for the cooperation of the whole society.

Following the presentation of the formal papers, Dr. A. J. Warren, chairman of the Committee on War and Post-War Tropical Medicine, presented in abstract its recently published recommendations which were later approved by the council and by the membership of the society in the general business session. These recommendations have been approved also by the United States Public Health Service.

At the joint meeting with the National Malaria Society, which was held on the morning of November 15, eleven papers were presented on various phases of malaria.

The annual dinner and business meeting of the officers and councilors of the society was held on Tuesday evening, November 14. All were in attendance at the meeting except Dr. Harold W. Brown and Colonel Charles F. Craig. The latter was prevented from attending owing to transportation difficulties. Former past presidents who attended the meeting included George C. Shattuck, E. B. Vedder, H. E. Meleney,

H. C. Clark, M. F. Boyd, E. C. Faust and N. P. Hudson. Dr. J. T. Culbertson represented the American Society of Parasitologists. Brigadier N. H. Fairley, director of medicine, A. I. F., an honorary member, was present at the council dinner as well as at the other sessions.

At the scientific session on Tuesday afternoon the presentation to Brigadier General James S. Simmons of the Walter Reed Medal[1] was made.

At the third scientific session the ninth Charles Franklin Craig Lecture entitled "Malaria in the Returning Serviceman" was delivered by Commander L. T. Coggeshall, U. S. Naval Reserve. This lecture will appear in a future issue of *The American Journal of Tropical Medicine.*

Informal talks were made at hospitality group sessions by Dr. W. A. Sawyer, who spoke on the United Nations Rehabilitation and Relief Administration; by Dr. N. H. Fairley, who spoke on certain aspects of malaria, and by Dr. H. C. Clark, who spoke on personal hygiene in the tropics. At the annual luncheon held on November 15, the address of the president, entitled "The Place of Tropical Medicine in International Health," was delivered.

Officers of the society were elected as follows: *President,* R. E. Dyer; *President-Elect,* J. S. Simmons; *Vice-president,* P. F. Russell; *Secretary-Treasurer,* J. S. D'Antoni; *Editor of the American Journal of Tropical Medicine,* C. F. Craig; *Councilors,* L. T. Coggeshall, G. R. Callender, J. F. Kessel, E. G. Hakansson, A. J. Warren, R. B. Watson, O. R. McCoy and E. I. Salisbury.

THE OKLAHOMA ACADEMY OF SCIENCE

THE thirty-third annual meeting of the Oklahoma Academy of Science was held at the Oklahoma Agricultural and Mechanical College, Stillwater, on December 2. There was an attendance of one hundred and thirty members. During the morning the biological, geological, physical and social sciences met in separate sections for the reading of scientific papers. Forty-five papers were presented before the various meetings. Following the noon luncheon, the retiring president, Dr. V. G. Heller, of the Agricultural and Mechanical College, gave an address entitled "Where Do We Stand in Nutrition?" A short business meeting preceded the address, during which officers for the following year were elected. During the afternoon, the Geological, Physical and Social Science Sections met together for a symposium dealing with the natural resources of the state. The section for the biological sciences met in separate session for a panel discussion on conservation.

[1] See SCIENCE, December 1, 1944, p. 490.

The new officers elected for the year 1945 are as follows:

President, J. Rud Nielsen (Physics), University of Oklahoma.

Vice-president, Section A, Biological Sciences, Dixie Young (Zoology), University of Oklahoma.

Vice-president, Section B, Geological Sciences, Ray L. Six (Geology), Oklahoma Agricultural and Mechanical College.

Vice-president, Section C, Physical Sciences, Edith Hammond (Chemistry), Oklahoma College for Women, Chickasha.

Vice-president, Section D, Social Sciences, T. H. Reynolds (History), Oklahoma Agricultural and Mechanical College.

Secretary-Treasurer, J. Teague Self (Zoology), University of Oklahoma.

Assistant Secretary-Treasurer, R. Chester Hughes (Zoology), Oklahoma Agricultural and Mechanical College.

AWARDS OF THE TELEVISION BROADCASTERS ASSOCIATION

AT the banquet on December 11 of the first annual meeting of the Television Broadcasters Association awards were presented as follows:

FOR TECHNICAL PIONEERING IN TELEVISION

First Award—Dr. Vladimir K. Zworykin, R. C. A. Laboratories, Princeton, N. J., in recognition of his "development of the iconoscope and the storage principle of picture pick-up, resulting in the first practical television pick-up equipment."

PROGRAM AWARDS FOR 1944

As the economic problem at present overshadows the artistic one these awards are made for contributions to the solution of the economic problems of programming.

First Award—Station WABD—Allen B. DuMont Laboratories, New York City, "for making its facilities available to all for study of the correlation of the economic and artistic problems of television production." Recipient, Sam Cuff, Station Manager.

FOR GENERAL CONTRIBUTION TO TELEVISION

This award is made for the summation of the efforts of many years.

First Award—General David Sarnoff, on leave from the presidency of the Radio Corporation of America, "for his initial vision of television as a social force, and the steadfastness of his leadership in the face of natural and human obstacles in bringing television to its present state of perfection."

SCIENTIFIC NOTES AND NEWS

DR. CHARLES FRANKLIN KETTERING, vice-president of the General Motors Corporation and general manager of its research laboratories, has been elected president of the American Association for the Advancement of Science.

COLONEL BRADLEY DEWEY, president of Dewey and Almy Chemical Company, Cambridge, Mass., formerly Rubber Director, has been elected president of the American Chemical Society for 1946. He will take office as president-elect on January 1, when Dr. Carl Shipp Marvel, professor of organic chemistry at the University of Illinois, becomes president, succeeding the late Thomas Midgley, Jr.

THE Edison Medal for 1944 has been awarded by the American Institute of Electrical Engineers to Dr. Ernst Fredrik Werner Alexanderson, consulting engineer of the General Electric Company, "for his outstanding inventions and developments in the radio, transportation, marine and power fields." The presentation will be made on January 24 at a joint session of the institute with the Institute of Radio Engineers during the Winter Technical Meeting, which will be held in New York from January 22 to 26. The Edison Medal, founded by associates and friends of Thomas A. Edison, is awarded annually for "meritorious achievement in electrical science, electrical engineering or the electrical arts" by a committee composed of twenty-four members of the American Institute of Electrical Engineers.

DR. OTIS W. CALDWELL, general secretary of the American Association for the Advancement of Science, was presented with the manuscripts for a brochure entitled "What's Ahead in Education?," prepared by his associates in educational experimentation and science teaching as a testimonial of their esteem and friendship on his seventy-fifth birthday. The presentation was made at a dinner at the Hotel Astor, New York City, on December 18.

PROFESSOR W. D. CAIRNS, of Oberlin College, for twenty-seven years secretary-treasurer and for the past two years president of the Mathematical Association of America, was elected on November 26 at the Chicago meeting honorary president for life.

THE following officers for 1945 were installed on November 7 at the fifth annual meeting of the Sigma Xi Club of Hawaii: *President,* Dr. C. K. Wentworth; *Vice-president,* Dr. F. G. Holdaway; *Secretary-Treasurer,* Dr. R. W. Hiatt; *Councilors,* Dr. W. B. Storey, Dr. F. P. Mehrlich and Dr. C. J. Engard, *ex officio.* The address of the retiring president was given by Dr. Engard, who is associate professor of botany at the University of Hawaii. It was entitled "The Concept of Homology in the Plant Kingdom."

DR. ARTHUR C. COPE, associate professor of chemistry at Columbia University, has been appointed professor of chemistry in charge of the division of organic chemistry of the Massachusetts Institute of Technology.

DR. PARKER D. TRASK, of the U. S. Geological Survey, has been appointed professor of geology in the University of Wisconsin. He will enter upon his new work in September, 1945, following completion of his present assignment on war work for the U. S. Geological Survey.

DR. C. WALTER CLARKE, executive director of the American Social Hygiene Association of New York, has been made clinical professor of public health practice at Harvard University.

DR. CHARLES A. DOAN, chairman of the department of medicine at the College of Medicine of the Ohio State University, has been appointed dean. Dr. Hardy A. Kemp has been made professor of public health and hygiene, the appointment to become effective on his return to the university from military service for which he now has leave of absence.

DR. LYLE R. DAWSON has been appointed professor of chemistry and head of the department at the University of Kentucky. On January 1 he will succeed Laurence L. Quill, who becomes a member of the faculty of Michigan State College at Lansing, Mich.

DR. ROLAND A. COULSON, who has returned from service with the Royal Air Force in Great Britain, where he was engaged in research for the Division of Nutrition of the Air Ministry, has been appointed instructor in the department of biochemistry of the School of Medicine of Louisiana State University.

DR. WILLIAM D. COOLIDGE will retire on December 31 as vice-president and director of research of the General Electric Company. Dr. C. G. Suits, assistant to the director, has been elected a vice-president of the company and has been placed in charge of the research laboratory.

DR. ZAY JEFFRIES, technical director of the lamp department at Cleveland of the General Electric Company, has been appointed, effective on January 1, vice-president of the company and manager of the chemical department.

DR. D. L. COTTLE has resigned as associate professor in chemistry at Rutgers University. He will join in January the Chemical Division of the Esso Laboratories.

PROFESSOR KNOWLES A. RYERSON, assistant dean of the College of Agriculture of the University of California, has returned from a year's leave of absence spent in establishing food production in the South and Central Pacific areas.

SEDGWICK C. ROGERS, who recently received the degree of Ph.D. in agricultural biochemistry at the Pennsylvania State College, has joined the research staff of the Forest Products Laboratory of the U. S. Forest Service at the University of Wisconsin.

DR. EGBERT MORLAND, since 1935 editor of *The Lancet*, has retired. He is succeeded by Dr. T. F. Fox, who will be the seventh editor since the periodical was first published in 1823. Dr. E. Clayton-Jones will be assistant editor.

IN testimony given on December 15 before the subcommittee on war-time health and education of the Senate, it was urged that private institutions receive Federal support for post-war long-range research. Those who testified included Dr. Henry S. Simms, of the College of Physicians and Surgeons, Columbia University; Dr. E. V. Cowdry, of Washington University, St. Louis; David Heyman, president of the Board of the New York City Public Health Research Institute; Dr. Lawrence S. Kubie, of Columbia University; Dr. Rolla E. Dyer, of the National Institute of Health; Colonel Cornelius P. Rhoads, of the Memorial Cancer Hospital, New York, and Admiral Harold W. Smith, of the office of the Surgeon General of the U. S. Navy.

DR. WARFIELD T. LONGCOPE, professor of medicine at the School of Medicine of the Johns Hopkins University, delivered on November 29 a lecture on "Allergic and Toxic Reactions to Sulfonamide Medication." This lecture was the first to be presented under the John Auer Lectureship founded by the Lambda Chapter of the Phi Beta Pi Fraternity at the School of Medicine of St. Louis University.

DR. VALY MENKIN, formerly of the Harvard Medical School, now of the department of pathology of the School of Medicine of Duke University, addressed on December 13 the Medical Group Conference of the University of North Carolina on "The Significance of Biochemical Units in Inflammatory Exudates."

THE annual fall lecture of the Society of the Sigma Xi at the University of Southern California was given on November 15 by Dr. Arthur H. Steinhaus, chief of the Division of Health Education and Physical Fitness of the U. S. Office of Education. His subject was "The Four Freedoms of Fitness."

THE Glenn L. Martin Aircraft Company has made a gift of $1,700,000 to the University of Maryland for education and research in aeronautical engineering. It is planned to establish the Glenn L. Martin College of Engineering and Aeronautical Science.

THE Mary Pemberton Nourse Fellowship in public health of Vassar College amounting to $2,500 will be awarded on April 1. The fellowship is offered to "a woman college or university graduate for original and outstanding work in public health at any approved institution," to provide for a year of study in the carrying forward of an original project or in writing on the subject.

THE department of pharmacology of the College of Medicine of Wayne University announces that two teaching fellowships are available for students who wish to obtain the degree of master of science in pharmacology. The fellowships carry a yearly stipend of $1,424 each. Applications and inquiries should be addressed to Professor Amedeo S. Marrazzi, chairman of the department, 1512 St. Antoine, Detroit 26, Mich.

THE name of the Athenaeum and Mechanics Institute of Rochester, N. Y., has been changed to the Rochester Institute of Technology.

THE following chemicals are wanted by the National Registry of Rare Chemicals of the Armour Research Foundation, 33rd, Federal and Dearborn Streets, Chicago 16, Ill.: l-amino-2-naphthol-4,6-disulfonic acid, 2,3,5-triamino benzoic acid, adenosine-5-pyrophosphate, o-amino benzaldehyde, boron trimethylammine, trifluoro acetic acid or esters, benzotrifluoride, 3-methyl-5-hydroxy benzoic acid, diallyl maleate and fumarate, 2,3-dihydroxy naphthalene-6-sulfonic acid, hyenic acid, isobutyl carbamate, methyl, ethyl, n-propyl or isopropyl azides, methyl nitrolic acid, molybdenum oxychloride, 3-nitro-4-chloro cyclohexylbenzene, nornicotine, phenyl carbamate, promin, sodium alpha naphthalene sulfonchloramide.

AT the University of Wisconsin research on penicillin is being carried on by three university departments. Members of the staff in charge are: in the department of biochemistry, Professors W. H. Peterson, M. A. Johnson and R. H. Burris; in the department of agricultural bacteriology, Professors E. M. McCoy and W. C. Frazier; and in the department of botany, Professors M. P. Backus and J. F. Stauffer. The work is being carried out under the auspices of the Office of Production, Research and Development of the War Production Board. It is in addition supported by grants from various companies which produce penicillin, including the Heyden Chemical Corporation, N. J., which has contributed $4,400, and Lederle Laboratories, Inc., Pearl River, N. Y., which has contributed $4,800. Funds have also been given by the Wisconsin Alumni Research Foundation.

BECAUSE of decreased enrolment and war conditions the Commissioner of Education, with the approval of the Governor, has decided to close temporarily the regular sessions of the State Teachers College at Hyannis as of August 31, 1944, and permit the Massachusetts Maritime Academy to use its facilities exclusively for the training of personnel for the Merchant Marine and the United States Navy, and for vocational training which may be related to the courses of instruction at the academy.

THE sum of $25,000 has been appropriated by the Michigan Legislature for research in forest products to be carried out by the Michigan Planning Commission.

COLUMBIA UNIVERSITY has received a gift from the Commonwealth Fund of $14,500 to be applied to the study of respiratory physiology in the department of medicine.

THE Toledo Hospital Institute of Medical Research of Toledo, Ohio, is the recipient of a grant made by the Snyder Ophthalmic Foundation of $6,500 per year for a period of two years for research on the physiology of the eye especially in relation to glaucoma. The grant will be extended for a longer period depending upon the results obtained in the first two years. Because of the war, research will be delayed until a physiologist with specialized training in the eye will become available.

THE Imperial Chemical Industries, Ltd., has made a gift to the University of Oxford of £7,200 a year for seven years to establish research fellowships in chemistry or physics. An electing committee will be appointed to carry out the objects of the gift.

CHARLES BROTHERTON, head of the Yorkshire chemical firm of Brotherton and Company, Limited, has agreed to subscribe £1,000 a year under deed for seven years for the establishment of a research fellowship in chemistry tenable at the University of Leeds, and a further £1,000 for seven years for a new lectureship in chemical engineering. In addition, he has subscribed £2,000 for the provision of the necessary extra equipment.

GROUND will soon be broken for the new hospital of the School of Medicine of Georgetown University, which will be erected directly to the east of the school. This structure will have a 400 bed capacity and has been planned with a view to eventual expansion to 600 beds. The project is being financed jointly by the Federal Works Administration and by the university.

DISCUSSION

ECHOLOCATION BY BLIND MEN, BATS AND RADAR

THERE are a number of situations where men or animals can not see clearly but nevertheless succeed in finding their way about by making sounds and detecting echoes from solid objects which are still some distance away. Many blind persons develop in the course of time a considerable ability to avoid obstacles by means of auditory cues received from sounds of their own making, such as footsteps or the tapping of a cane. Their skill can be drastically impaired by ear plugs or by distracting noises.[1, 2] Bats can fly through the total darkness of caves without striking the walls or the jutting stalactites which may complicate their path. The bats emit a supersonic cry (inaudible to human ears because its frequency is from 30,000 to 70,000 c.p.s.) and orient themselves by means of the echoes of this cry which return to them from any obstacles which lie ahead.[3, 4, 5]

Since there is no convenient term available to describe this process of locating obstacles by means of echoes, I suggest the word *echolocation*, not only for the abilities of bats and blind men, but for several other analogous cases which I shall mention below. The meaning of this word, and a corresponding verb *to echolocate*, are likely to be clear when first heard or read, since they are formed simply by joining *echo* and *locate*. It seems best to accent the first syllable in order to make clear that the word echo is employed. These terms would fill a definite need, since they describe an important and general process for which one otherwise requires long phrases or whole sentences.

Man has developed instruments for echolocation which are far more effective than the blind man's tapping cane. In fog-bound coastal waters the captain of a ship often blows his whistle and listens for an echo from cliffs or rocks which he suspects are near. Even such small objects as buoys are said to be detected in this way by men with long experience. The depth of water under a ship's hull is often measured by the sonic depth-finding apparatus or fathometer, an instrument which sends down sound waves through the water and measures its depth by timing the returning echoes. This same instrument has also been used by fishermen to echolocate schools of fish beneath their vessel.[6] Submarines are detected by apparatus work-

[1] S. P. Hayes, "Contributions to a Psychology of Blindness," 49–63, 1941.

[2] M. Supa, M. Cotzin and K. M. Dallenbach, *Am. Jour. Psych.*, 57: 133–183.

[3] H. Hartridge, *Jour. Physiol.*, 54: 54–57, 1920.

[4] D. R. Griffin and R. Galambos, *Jour. Exp. Zool.*, 86: 481–505, 1941.

[5] R. Galambos, *Sci. Monthly*, 56: 54–57, 1943.

[6] A. L. Tester, Bull. 83, Fisheries Res. Board of Can., Ottawa, 1943.

ing on the same basic principles, although the developments by which such devices have been perfected are not made public for obvious reasons.

Nor is the process of echolocation limited to sound waves. The "absolute" or radio altimeter used in airplanes is the counterpart of the fathometer except that radio waves are employed as the "probing" signal. A radio signal is sent out from the airplane and electronic devices measure the time required for this signal to be reflected back as an echo, either from the ground below the airplane or from a mountain ahead of it.

Finally we have radar, a refinement of the radio altimeter so beautifully perfected that it can echolocate airplanes at great distances by sending out radio waves and picking up the reflected energy returning from the distant aircraft. It would be presumptuous for a biologist to discuss radar in detail, even if information were available; but it does seem clear that the same fundamental process is involved in all these phenomena, from the bat's supersonic cries and the blind man's tapping cane to the intricacies of radar.

Echolocation may be employed in still other situations. Owls or flying squirrels, for instance, could use it to advantage, and future studies may disclose that they have evolved some variant of the bat's method of finding its way about. Unsuspected forms of echolocation may be found in nature or developed by human technology, and the use of a single unifying term can help clarify our ideas and stimulate such future developments.

DONALD R. GRIFFIN

BIOLOGICAL LABORATORIES,
HARVARD UNIVERSITY

MORTALITY AMONG GEOLOGISTS

IN SCIENCE for May 26, 1944, there appears a short article by Professor William H. Hobbs under the title "Unusual Mortality among Geologists." This is interesting but perhaps of very little scientific value, and Professor Hobbs's suggestion that the war may be responsible for the phenomenon seems a bit far-fetched. Another explanation seems more reasonable.

Professor Hobbs has taken a period of a little over five months, from November 16, 1943, to April 19, 1944, and finds that sixteen fellows of the Geological Society of America died during that period. I have no statistics at hand as proof, but I believe these winter months are much more hazardous to elderly people than the summer months. Professor Hobbs does not compare the total for this five-months period with similar periods of the past, but with annual totals. Only two of these sixteen deaths occurred in 1943, so if we stick to annual totals it is quite probable that 1943 will show nothing unusual, but 1944 may easily show a high. But is there any reason why it should not? Every phenomenon which shows variations must have highs and lows, and some high is bound to be greater (or equal to) any other high. It might easily be that 1944 will show one of those highs in the death-curve of fellows of the Geological Society of America.

The ages of these sixteen deceased fellows range from sixty-four to ninety-four. This means that they were in college roughly from 1870 to 1900. Now it is well known that that was the period in which students were turning from the classical studies to science and engineering. That was the time when the number of students in the colleges and universities, especially in the Mid-west, increased by leaps and bounds, and that was the time when great geologists like Thomas C. Chamberlin, Joseph Le Conte and John C. Branner, to mention only three under whose influence I happened to come, flourished and attracted many students to their classes. It is not surprising but inevitable that some fifty or sixty years after those sixteen fellows were in college there should be a maximum in the death curve of geologists. $\frac{1}{2}(1870 + 1900) + 59 = 1944$. It may be permissible to point out what appears to be a small error in the article under consideration. The last name in the table of deceased fellows is that of R. C. Wells. In the second paragraph below there are given the names of three geologists, not fellows of the Geological Society, who died during the period under consideration. R. C. Wells is one of these names. Of course there might have been two geologists of the same name and initials who were born and died on the same days, but the probabilities in favor of such an event would seem to be rather small.

If we want to be sticklers for accuracy, then the name of F. B. Hanley should not have been included among the three geologists because he died on April 24, which was after the period under consideration.

The suggestion of Professor Hobbs that the phenomenon considered might be laid to the war seems almost fantastic. Most of these men were too old to have sons in the present war and it seems highly improbable that worry over the destruction of cultural institutions and values could have played more than a very minor role in the case.

Why drag in the war to explain what appears to be a perfectly natural phenomenon taking place in the orderly course of events?

SIDNEY D. TOWNLEY

STANFORD UNIVERSITY

REVISTA SUDAMERICANA DE MORFOLOGIA

THIS *South American Review of Morphology* is a new biennial publication of great scientific value

which aims to publish, beginning with its 1943–44 volume, all the most important original contributions, in Spanish and Portuguese, relating to anatomy, pathological anatomy, comparative anatomy, histology, anthropology and embryology, and bearing an intimate relation to morphology.

It is clear that such a publication has come to fill a long felt need in South America where biological and medical research has made remarkable progress in recent years and, by not restricting its scope to highly specialized lines of endeavor, ought to appeal to a large number of readers, both in South America and elsewhere, thus fulfilling its double purpose of disseminating the results of local research and of promoting a truly Pan-American spirit of scientific collaboration.

Finally, it ought to be pointed out that the editorial board, headed as it is by the well-known names of Professors A. E. Bianchi, of Argentina; M. de Freitas Amorim, of Brazil, and E. Herzog, of Chile, and including two representatives of each of the South American Republics, is a guarantee of the high quality and broad scope, both scientific and geographic, of the articles to come.

It is hoped that a number of scientists and scientific organizations in the United States will subscribe to this journal, the cost of which is $5.00 per year. All correspondence regarding the journal should be addressed to Professor Bianchi, Córdoba 827, Buenos Aires, Argentina.

COMMITTEE ON INTER-AMERICAN SCIENTIFIC PUBLICATION, HARVARD COLLEGE OBSERVATORY

FURTHER REMARKS CONCERNING THE U.S.S.R. ACADEMY OF SCIENCES

IN reply to the criticisms of Dr. S. P. Timoshenko and Dr. J. V. Uspensky, of Stanford University, to my paper entitled "History and Activities of the U.S.S.R. Academy of Sciences during the Past Twenty-Five Years," published in SCIENCE for June 2, I wish to make the following remarks relative to their paper published in the issue of September 1.

It is still maintained that Newton's philosophy was opposed by leading Russian scientists at the time of the founding of the Russian Academy of Sciences and that what was done in Western Europe in the seventeenth and the beginning of the eighteenth century was accomplished in Russia nearly two centuries later.[1] In France the first appearance of Newton's "Principia" of 1687 caused the adherents of Descartes' philosophy of vortices considerable speculation; but in spite of this, Newton was rapidly accepted in France, Holland and Germany. Scientific progress is universal and therefore must be measured in terms comparable to universal history and not nationalistic progress. Fifty years in the history of science is indeed a brief period measured, as a unit, from the time of the origin of the ancient Egyptian civil calendar, 4236 B.C.[2]

However, the main contention of my remarks was, What caused the delay of approximately two hundred years before Newton's "Principia" was published in Russia?

I am under great obligation to my friend and colleague, Mr. Anatol J. Shneiderov, of The George Washington University, for examining a recent publication of the U.S.S.R. Academy of Sciences commemorating in Moscow, 1943, the three hundredth anniversary of Newton's birth. We find the following by A. D. Lublinskaya: "In 1688 the *Journal des Savants* recognized that Newton's 'Principia' gives a better explanation of the mechanics of planetary motion. In 1690 Huygens (Holland) in his 'Traité de la lumière' analyses the 'Principia' and agrees with Newton's thesis of mutual gravitation as irreproachable. From 1691–1725 violent polemics continued between the formally recognized Newtonian mechanism and the Descartian theory of vortices." But Voltaire's influence sounded the end of this verbal warfare.

In Russia the name of Newton was first mentioned in the *Proceedings of the Russian Academy of Sciences* in 1725, where it is mentioned that the Russian academician Bülfinger opposed Newton's point of view concerning polar flattening of the earth, because according to the knowledge of the time the sphericity of the earth had not yet been proven. Again in 1726 Newton's name was mentioned in connection with some physical experiments performed by Bülfinger. From 1727 to 1747 there is no record relating to Newton's work, or commentaries; but in 1748 Lomonosov in his letter to Euler opposes Newton in regard to the identification of mass and weight. In 1751, not 1752, Clairnaut's "La Théorie de la lune" received the official prize of the Russian Academy of Sciences. This would seem to indicate that Russia acknowledged and paid homage to France and Clairnaut and not to England and Newton. Professor Krylov further states that Lomonosov, in 1756, opposes Newton's theory of light, and in 1760 criticizes Newton's theory of gravitation as a fundamental property of matter. Lomonosov was the founder of Russian scientific thought and a follower of Cartesian doctrines. His consequent influence in opposing the Newtonian philosophy can not be disregarded.

[1] Krylov's translation of the "Principia."

[2] Tyler's "History of Science." (Or, more definite, when man first had concepts of the meaning of air, fire, water and earth, and found a basis for some logical system of definition and classification.)

The formal recognition of Newton's philosophy in 1916 by Professor Krylov's translation is the first definite public recognition history records. During the first one hundred years of the academy's life no English scholar or man of science was honored by membership. Newton was still alive during the first two years of the academy's existence. The translation of Newton's "Principia" by Professor Krylov was made from the fifth edition,[3] as he states, not the third, as Dr. Timoshenko and Dr. Uspensky state. In regard to my mention of the first edition, this is referred to on the title page of the new Russian edition of the "Principia."

Referring to the quotation of Professor Petrunkevitch's statement, I think it would have been much fairer to their national pride not to have reshuffled Professor Petrunkevitch's quotation, taking some part of it and bracketing it into another part, thus giving the reader the wrong impression. My effort was to bring out from this quotation something to the credit of Russian scientific training.

My source for the information concerning Nicholas and Daniel Bernoulli was "Tableau Général . . . dans les Publications de L'Académie Impériale des Sciences de St.-Pétersbourg, 1872," 1st part, pages 408–409. Under the heading of Membres Effectifs, it is stated that both Bernoullis were professors of mathematics in the academy. Nicholas was born in Basel, Switzerland, and Daniel in Groningue (in my paper I stated the latter was from Germany, which was an error.) Daniel did study medicine, but never practiced until after he retired from the academy. Drs. Timoshenko and Uspensky state that Goldbach was never a member of the academy. According to the last reference quoted on page 408 he was a "membre effectif" and was the first "Secrétaire de Conférence de l'Académie."

FREDERICK E. BRASCH,
Consultant in the History of Science,
Library of Congress

SCIENTIFIC BOOKS

ELEMENTARY STATISTICS

Elementary Statistics. By MORRIS BLAIR. xiv + 690 pp., including 98 plates. Henry Holt and Company. 1944.

NEW developments in statistical methods are leaving their impact on pure science, manufacturing development, marketing and business practice, public opinion and government statistics, and accordingly attention is demanded from all branches of science when a new book on statistics appears. To the pure scientist, and to most readers of SCIENCE, their main concern is just what statistical practice has to do with scientific method. It is not realized by pure scientists in general that the statistical method over the past few years has brought about a revolution in the concepts of what is meant by exact sciences. Perhaps the "exact scientists" themselves are not under delusion with regard to what constitutes the so-called "exact sciences," but the delusion is certainly common in other places. Actually there is no such thing as exactness in the sense of exact reproducibility of results. While many scientists may agree with W. O. Willcox in the June issue of the *Journal of the American Society of Agronomy* that the result of an applied force "must be accepted as an absolute value and wholly reproducible under parallel conditions without margin for chance," all will agree that there is a hitch in it; the conditions of trials can not be kept constant, and the statement in practice can not be verified. One must recognize the inherent variability of all measurable phenomena. There is no such thing as constancy of measured results except in the sense of statistical control, a concept introduced by Shewhart in 1926. The concept of exactly reproducible results is now replaced, through the work of Shewhart, by the concept of statistical control or the constant cause system. A constant cause system produces not constant results, but constant variability, in the sense that on the basis of past results produced by the constant cause system, rational and dependable predictions can be made with regard to the proportion of the next 100 or 1,000 observations that will fall within any given pair of limits. In other words, probability theory applies to a phenomenon in a state of statistical control.

The statistician recognizes two kinds of variability: (1) variability that can be eliminated (arising from "assignable" causes), and (2) variability that can not be altered (arising from "chance" causes) without installing a fundamentally new cause system. The second type of variability exhibits statistical control. Whether a state of statistical control exists is decided by use of the control chart and the Shewhart criterion of randomness. As Shewhart states in his book, "The Statistical Method from the Viewpoint of Quality Control" (Graduate School, U. S. Department of Agriculture, 1939) the constant cause system represents the limiting state of knowledge.

Controlled variability is practically all contained within an "error band," which can be calculated from

[3] Sir Isaac Newton's Principia reprinted for Sir William Thomson, LL.D., Glasgow, James Maclehose, Publisher to the University. MDCCCLXXI. 4to. [According to Professor Krylov.]

a series of past observations. Ordinarily, a decrease in the spread of the error band can be attained only at a price. In practical work there is a limit in precision beyond which the precision gained is not worth the additional cost. Part of the statistician's job is to design sample surveys that produce the precision required for the purpose (formulation of action), but no more.

The simplest arrangement of the constant cause system is a smooth bowl in which have been placed physically similar discs on which numbers have been written. Samples drawn blindfolded therefrom with proper care in mixing and replacement will show variability that meets the criterion of statistical control. This variability can not be altered without the introduction of new numbers on the disks. Statistical control can be achieved in manufacturing and in sampling in the social science, though the emphasis must be on the word "achieve." Statistical control is not ordinarily found to exist naturally but requires effort, to which incidentally the work of Shewhart has been largely directed; his methods not only tell when control has been achieved but they help to achieve it.

The book under review can be said to bring the subject of statistical methodology to the reader as it was perfected up to the impact of Shewhart researches. The principles of the newer methods in statistics have appeared in at least one elementary text-book, namely, Colonel Leslie E. Simon's "An Engineers' Manual of Statistical Methods" (Wiley, 1941), and the principles are being put into sampling practise in both government and industry.

In the reviewer's opinion, the science of statistics will rise rapidly in the eyes of the natural scientists when in the future three conditions are met: (1) when it is recognized that the purpose of collecting, compiling and analyzing data is to provide a rational basis for formulating a course of action; (2) when the concept of the constant cause system and the usefulness of the statistical method in detecting assignable causes of variability is recognized; and (3) when the statistician is recognized as an expert in measuring and discovering assignable cause of variability, and in deciding how much precision (how big a sample) is economical.

The author of this book states in one of the prefaces directed to teachers that his product is a result of fifteen years of teaching, and that he has sifted the material very carefully. He states also that the business man and practising statistician will find the text valuable as a reference book. Certainly the author's claims in these respects are admirably fulfilled so far as the book goes. The summary formulas at the end of the book (pp. 624 *ff.*) are extremely handy for reference. The leading questions and references at the end of each chapter will likewise draw appreciation from studnts, teachers and practising statisticians, as well as casual users. The practising statistician must be concerned not only with the science but the art of his subject, and the frequent suggestions for forms or work sheets and tables will be duly appreciated by many users.

What is needed in statistical theory and practice is some arrangement for interchange of talent between universities, government and industry. Some day, sometime, arrangements will be worked out whereby writers having the gift of presentation like Mr. Blair and the enthusiasm to write text-books, can have interneships in government and industrial practise.

W. EDWARDS DEMING

BUREAU OF THE BUDGET,
WASHINGTON

FORESTRY

Forestry on Private Lands in the United States. By CLARENCE F. KORSTIAN, Duke University, School of Forestry, Bulletin 8, June, 1944; 234 pp. 27 figs. Price, paper $1.00; cloth, $1.50.

KORSTIAN'S study of the field of private forestry in the United States constitutes a sincere and impartial investigation of a subject on which little conclusive factual evidence of an authoritative character exists despite its importance in our economic future. Deep public concern has been manifested since the origin of the forestry movement in the '80s and '90s of the last century, over the progressive denudation of virgin forests, with little thought given to their renewal and perpetuation by private owners and operators. Although predictions of an impending timber famine, prevalent before World War I, have failed to materialize with the expected rapidity, due to the unexpected development of substantial quantities of second growth conifers in the vast southern pineries, yet the U. S. Forest Survey has lent no encouragement to the belief that scarcity of wood at an approaching future period will be avoided.

Consequently, public attention has again been focused on the problem of private forest lands, which comprise nearly 73 per cent. of all commercially productive lands, but which are being cut in the proportion of 95 per cent. of the total yield of saw-timber. Are private owners changing their attitude toward their forest holdings and managing them by methods which will insure the reproduction and maintenance of this resource, or is the process of exploitation, liquidation and denudation continuing? If it is, what should be done about it?

Dr. Korstian approaches this question in two ways. His primary purpose is to determine, by a process of sampling, the extent and character of private forest management based on individual initiative. His sec-

ond, is to explore public opinion in its reactions to the problem, and its cure.

For this purpose eight key states were studied. For the northeast, New York; for the Lake States, Michigan and Wisconsin; in the South, Virginia, Alabama and Arkansas; and for the Pacific Northwest, Oregon and Washington.

In his analysis of the physical situation, Korstian briefly describes the important forest types and their present condition, the forestry measures which have been attempted, with especial reference to silviculture, and finally, gives examples of owners and operators who have adopted and are practicing forest management with the object of sustained, perpetuated yield from their holdings. No attempt could be made to present statistical summaries which would show the extent or degree to which these practices had superseded liquidation or satisfied future requirements, on a national or regional scope. It does serve to reveal a marked and extensive trend away from past short-sighted indifference, towards permanent private management of forests.

The results of Korstian's second line of investigation, into the state of public opinion, reveals a definite trend of support for the antidote of public regulation of private cutting. But equally prevalent was the sentiment that such measures if found necessary should be left in the hands of state authorities, rather than centralized at Washingon, D. C. Due emphasis is placed on the need for adequate control of forest fires, and continuance of federal aid under the existing cooperative plan embodied in the Clarke McNary law. Emphasis is also placed on expansion of public educational programs, cooperative assistance to owners, and extension forestry, especially as applied to the farm woodlands which alone embrace almost exactly 30 per cent. of all commercial forest land.

H. H. CHAPMAN
NEW HAVEN, CONN.

REPORTS

THE ARCHBOLD BIOLOGICAL STATION

IT is announced by the Archbold Expeditions of the American Museum of Natural History that use of the facilities of the Florida station, previously reserved to staff members of the American Museum, will now be extended to a limited number of approved workers from other scientific institutions. The facilities will be available to workers in any field of biological research. A nominal charge to cover living and other expenses is contemplated, but the matter of cost relationships is left open for consideration in accordance with the requirements and circumstances of the studies of each individual.

The Archbold Biological Station is located at the southern end of the hill and lake region of peninsular Florida, about 25 miles south of Sebring and 32 miles west of Okeechobee. Established in 1941, it is maintained by Archbold Expeditions, an incorporated non-profit organization headed by Richard Archbold, research associate in the Department of Mammals at the American Museum. The establishment of the station was made possible through the generous gift by John A. Roebling of a thousand-acre estate, highly improved with service buildings, complete with working and maintenance plant and free of all encumbrance.

The original purpose of Archbold Expeditions was biological exploration in the Indo-Australian region, with emphasis on mammals, birds and plants. In the prosecution of this work, outstandingly successful expeditions were made to British New Guinea in 1933–1934 and 1936–1937, and to the Snow Mountains of Dutch New Guinea in 1938–1939. When in 1940 it became apparent that, owing to disturbed political conditions in the Pacific, plans already maturing for another New Guinea expedition would have to be postponed indefinitely, attention was turned to related projects realizable in the United States. In the spring and early summer of that year, bird and mammal life history and behavior studies, and field experiments in color moving pictures and sound recording, were carried out in the southwestern deserts near Tucson, Arizona.

The Florida station was established to serve as a permanent home base for the expedition organization, and with the object of carrying out and aiding biological research in the United States. As opening projects, faunal surveys of the mammals and birds of the station and vicinity were made by A. L. Rand and Per Höst, members of the expedition staff. Rand also made studies in the life history and development of behavior of the burrowing owl, the Florida jay and other birds, in continuation of his well-known work in this field. Höst, now in war service, directed his attention to life history studies of the beach mouse and the spotted skunk, and research into the mechanism involved in color change in the plumage of birds, supplementing his field work with moving pictures of Florida wild life in color.

In 1943, various research projects were carried out at the station by staff members of the American Museum, working on a visiting fellowship basis. Included in these projects were life history studies of the round-tailed muskrat by John Eric Hill, collections of insects and spiders by Mont A. Cazier, life history studies of the Florida jay by Dean Amadon

and collections of ants and study of the ecology and behavior relations of the stump associations of ants and termites by T. C. Schneirla. During the spring and summer of the current year, Schneirla continued his investigations at the station. The late Henry C. Raven used the laboratory facilities for work toward the completion of his monograph on the anatomy of the gorilla. Raymond B. Cowles, of the University of California, and Charles M. Bogert conducted investigations into the thermal requirements of reptiles, in continuation of research first undertaken in the California deserts in 1939. Edwin H. Colbert made the station his headquarters for study of a subtropical environment in relation to interpretations involving faunal relationships and former ecological conditions of extinct vertebrates, combined with field and laboratory observations on living crocodilians.

The results of much of the foregoing work at the station have been, or will be, published in *Novitates* and the *Bulletin* of the American Museum of Natural History, as part of a subsidized series called "Results of the Archbold Expeditions," of which 51 numbers have appeared to date.

Probably no other locality, and certainly no other established station in southern Florida, offers such a variety of interest for zoological, botanical and ecological research. The station itself presents a rather uniform and long undisturbed sand-scrub habitat of oaks, saw-palmetto, sand-pine and slash-pine, but being centrally situated in a rich and diversified country, it gives easy access to other habitats such as pine flatwoods, bay-gall and cypress swamps, hardwood and cabbage-palm hammocks, dry prairies, wet prairies, freshwater swamps, streams, canals and lakes. A rich representation of wading birds and water birds in the area surrounding the station, and nesting concentrations of herons, egrets and ibis, accessible for observation and experiments, are of special interest to the ornithologist. The station is well equipped not only for the types of research that have been carried out there in the past but for an expanded program. There are provisions for the maintenance of small animals in captivity and large rooms for work indoors. Laboratory equipment includes microscopes, microtome and apparatus for quantitative and qualitative analysis. There are a very complete photographic laboratory and an excellent machine shop. Motor transport is available up to the limit imposed by wartime restrictions.

In matters concerning research at the station, Archbold has the assistance of an advisory board consisting of H. E. Anthony (*chairman*), F. A. Beach, L. J. Brass, Per Höst, Robert Cushman Murphy and H. F. Schwarz, all at the American Museum, and A. L. Rand, at the National Museum, Ottawa. Inquiries from individuals or institutions interested in presenting programs involving research in specific problems which could with advantage be carried out at the station may be sent to Richard Archbold, Box 1309, Lake Placid, Florida, or to any member of the advisory board. Suggestions setting forth ideas for the development of the full potentialities of the station will be welcomed, and given every consideration in plans for the advancement of the aims to which the station is dedicated.

L. J. BRASS

SPECIAL ARTICLES

THE Rh SERIES OF ALLELIC GENES[1]

WITH the aid of the three major varieties of human anti-Rh agglutinins, five variants of the Rh agglutinogen have been identified.[2, 3, 4] According to the writer's genetic theory,[5] which is now established,[6] these blood properties are inherited by a series of six allelic genes, Rh_1, Rh_2, Rh', Rh'', Rh_0 and rh, named after the agglutinogens which they determine. These observations have been substantiated in full by Race *et al.*,[7, 8] working independently, who have in addition defined the reactions given by each Rh variant with so-called anti-Hr[9] or anti-St[10] sera. Moreover, Race *et al.* have partially defined another variant of the Rh agglutinogen, determined presumably by a special allelic gene,[11] tentatively designated Rh_y. As was mentioned in one of the earlier papers by the present writer,[5] occasional bloods have been encountered in our work which give intermediate reactions, suggesting the existence of several additional variants of the Rh agglutinogen. The writer now believes that some of these atypical types are determined by special allelic genes, one of which possibly corresponds to the Rh_y gene of Race *et al.* As will be shown in this re-

[1] From the Serological Laboratory of the Office of the Chief Medical Examiner of New York City. Aided by a grant from the Carnegie Foundation through the Committee on Human Heredity of the National Research Council.

[2] A. S. Wiener and K. Landsteiner, *Proc. Soc. Exp. Biol. and Med.*, 53: 167, 1943.

[3] A. S. Wiener, SCIENCE, 98: 182, 1943.

[4] A. S. Wiener and E. B. Sonn, *Jour. Immunol.*, 47: 461, 1943.

[5] A. S. Wiener, *Proc. Soc. Exp. Biol. and Med.*, 54: 316, 1943.

[6] A. S. Wiener, E. B. Sonn and R. B. Belkin, *Jour. Exp. Med.*, 79: 235, 1944.

[7] R. R. Race, G. L. Taylor, K. E. Boorman and B. E. Dodd, *Nature*, 152: 563, 1943.

[8] R. R. Race, G. L. Taylor, D. F. Cappell and M. N. McFarlane, *Nature*, 153: 52, 1944.

[9] P. Levine, *Jour. Ped.*, 23: 656, 1943.

[10] R. R. Race and G. L. Taylor, *Nature*, 152: 300, 1943.

[11] R. R. Race and G. L. Taylor, *Nature*, 153, 560, 1944.

port, the newer designations[12] of the Rh antisera and Rh genes have greatly simplified the problem of nomenclature for the "intermediate" genes.

The six standard allelic Rh genes and the reactions that they determine with the three varieties of anti-Rh sera, and with anti-Hr (or anti-St) sera, are shown in Table 1.

TABLE 1
THE Rh GENES

Genes[13]	Reactions with antisera: anti-Rh$_0$ (85 per cent. pos.)	anti-Rh′ (70 per cent. pos.)	anti-Rh″ (30 per cent. pos.)	Anti-Hr (St)[14]
rh	Neg.	Neg.	Neg.	Pos.
Rh$_1$ (*Rh*$_0$′)	Pos.	Pos.	Neg.	Neg.
Rh$_2$ (*Rh*$_0$″)	Pos.	Neg.	Pos.	Pos.
Rh$_0$	Pos.	Neg.	Neg.	Pos.
Rh′	Neg.	Pos.	Neg.	Neg.
Rh″	Neg.	Neg.	Pos.	Pos.

As has already been mentioned, occasional bloods were encountered which gave weak or intermediate reactions with one or more of the Rh antisera. For the sake of simplicity, in our previous reports, these weak reactions were disregarded and all bloods were classified under one of the eight types[15] as determined from the stronger reactions. Now that sufficient evidence has accumulated to establish the theory of the six major allelic genes, more attention has been focussed on the "intermediate" types, and it appears that some of these, at least, are also determined by special allelic genes. A few examples of these rare intermediate types are given in Table 2, and it will be seen that they

TABLE 2
"INTERMEDIATE" Rh GENES

Intermediate types	Reactions with antisera: anti-Rh$_0$	anti-Rh′	anti-Rh″	Formerly classed together with major types:
Rh$_1$(″)	Pos.	Pos.	Weak	Rh$_1$
Rh$_2$(′)	Pos.	Weak	Pos.	Rh$_2$
Rh$_0$(″)	Pos.	Neg.	Weak	Rh$_0$
Rh$_{(0)}$′	Weak	Pos.	Neg.	Rh′

enlarge considerably the series of Rh allelic genes. In selecting designations for the intermediate types and genes, the writer has merely extended the principles employed for naming the major types, with the qualification that all weak or intermediate reactions are indicated by parentheses.[16]

That the intermediate types described are actually determined by special genes can of course be established with certainty only by the investigations of family material. For example, the family of Table 3

TABLE 3
FAMILY ILLUSTRATING TRANSMISSION OF GENE Rh$_{(0)}$′

Blood of	Group and M–N type	Reaction with Rh antisera: anti-Rh$_0$	anti-Rh′	anti-Rh″	Rh Type	Formerly classified as
Mother	OM	±	++	–	Rh$_{(0)}$′	Rh′
Children						
Twin daughter A	OM	±	++	–	Rh$_{(0)}$′	Rh′
Twin daughter B	OM	±	++	–	Rh$_{(0)}$′	Rh′
Daughter	OM	±	++	–	Rh$_{(0)}$′	Rh′
Daughter	OM	++	++	–	Rh$_1$	Rh$_1$
Son	OM	++	++	–	Rh$_1$	Rh$_1$

(father not living) illustrates the hereditary nature of the intermediate type Rh$_{(0)}$′.

Table 4 illustrates the hereditary nature of type

TABLE 4
FAMILY ILLUSTRATING TRANSMISSION OF GENE Rh$_1$(″)

Blood of	Group and M–N type	Reactions with antisera: anti-Rh$_0$	anti-Rh′	anti-Rh″	anti-Hr	Rh type	Most probable genotype
Mother ...	A_2M	++±	++±	+	+±	Rh$_1$(″)	*Rh*$_1$(″)*rh*
Children:							
Daughter*	$A_{1,2}M$	++±	++	+	–	Rh$_1$(″)	*Rh*$_1$(″)*Rh*$_1$
Son	$A_{1,2}M$	++±	++	++±	++	Rh$_1$Rh$_2$	*Rh*$_1$(″)*Rh*$_2$
Daughter	$A_{1,2}M$	++±	++±	+	–	Rh$_1$(″)	*Rh*$_1$(″)*Rh*$_1$
Son	A_2M	++±	++	+	–	Rh$_1$(″)	*Rh*$_1$(″)*Rh*$_1$

* Mother of an erythroblastotic baby,[17] and having anti-Hr agglutinins in her serum.

Rh$_1$(″), determined by the corresponding gene *Rh*$_1$(″), which may be the same as the gene *Rh*$_y$ of Race *et al.*

Unfortunately, in this family also the father was not alive, but his probable Rh-type (Rh$_1$Rh$_2$) can be surmised from the types of the mother and children.

It should be mentioned that the anti-Rh′ and anti-Rh″ sera used in these studies were really anti-Rh$_0$′ and anti-Rh$_0$″ sera with weak anti-Rh$_0$ agglutinins whose action was eliminated by simple dilution. Recent studies reveal that some bloods containing Rh$_0$ factor react distinctly with traces of anti-Rh$_0$ agglutinin insufficient to clump other bloods containing the

[12] A. S. Wiener, SCIENCE, 99: 532, 1944.

[13] The alternative designations, *Rh*$_0$′ and *Rh*$_0$″ are used whenever necessary for the sake of clarity. As a rule, the simpler designations, *Rh*$_1$ and *Rh*$_2$, will be found preferable and unambiguous.

[14] Recently, through the courtesy of Dr. I. Davidsohn, an anti-Hr (St) serum became available to the writer and it was possible to corroborate Race and Taylor's report (*Nature*, 152: 300, 1943) concerning the properties of such antisera.

[15] Of the eight Rh types, the theoretically rarest type, Rh′Rh″, until recently had not been encountered. F. Stratton (*Nature*, 153: 773, 1944) now reports finding four such individuals, two of them siblings.

[16] An alternative method of indicating the intermediate reactions is with the aid of dots. The four types listed in Table 2 would then be designated as Rh$_1$··, Rh$_2$·, Rh$_0$·· and Rh·′ respectively.

[17] I. Davidsohn, E. Potter and A. S. Wiener, unpublished case.

Rh_0 factor. In this way reactions could occur due to residual anti-Rh_0 agglutinins in the serum, which might erroneously be attributed to the anti-Rh′ or anti-Rh″ agglutinin. This pitfall can now be eliminated with the aid of potent anti-Rh_0 blocking serum,[18] because if such a serum is mixed with a diluted anti-Rh_0′ or anti-Rh_0″ serum, the action of the anti-Rh_0 agglutinin will be completely eliminated. An alternative technique is to retest the blood sample with the anti-Rh′ and anti-Rh″ sera after the blood has been treated with anti-Rh_0 blocking serum in order to block the Rh_0 antigen.

The author feels that these observations concerning the intermediate genes probably complete the picture of the Rh blood types. Should, however, other Rh antisera be encountered with specificities different from those of the known antisera, it should not be too difficult to adjust the nomenclature in order to include them in the scheme. For example, if a new agglutinin anti-Rh‴ is discovered, analogous to anti-Rh′ and anti-Rh″, it would only be necessary to postulate the existence of two additional genes Rh_3 (or Rh_0''') and Rh''', and the scheme of 8 Rh types would be enlarged to a scheme of 14 types as shown in Table 5.

TABLE 5

SCHEME OF THE RH TYPES EXTENDED TO INCLUDE A HYPOTHETICAL AGGLUTININ ANTI-RH‴

Blood lacking Rh_0					Blood containing Rh_0				
	Reactions with antisera					Reactions with antisera			
Types	Anti-Rh′	Anti-Rh″	Anti-Rh‴	Anti-Rh_0	Types	Anti-Rh′	Anti-Rh″	Anti-Rh‴	Anti-Rh_0
Rh-neg.	−	−	−	−	Rh_0	−	−	−	+
Rh′	+	−	−	−	Rh_1 (Rh_0′)	+	−	−	+
Rh″	−	+	−	−	Rh_2 (Rh_0″)	−	+	−	+
Rh‴	−	−	+	−	Rh_3 (Rh_0‴)	−	−	+	+
Rh′Rh″	+	+	−	−	Rh_1Rh_2	+	+	−	+
Rh′Rh‴	+	−	+	−	Rh_1Rh_3	+	−	+	+
Rh″Rh‴	−	+	+	−	Rh_2Rh_3	−	+	+	+

As has been pointed out elsewhere,[19] the anti-Hr sera have a place in the scheme of the Rh blood types similar to that of the anti-O sera in the blood group scheme. The newer knowledge of the Hr factor[20] has therefore helped to clarify the problem of the nature of the anti-O sera. If, as seems probable, anti-O sera react with the properties determined by genes O and A_2, but not with those determined by genes A_1 and B, then it is clear that only bloods of genotypes A_1B, A_1A_1 and BB will fail to react with potent anti-O sera (*cf.* Table 6). The confusion that existed up to now

[18] A. S. Wiener, *Proc. Soc. Exp. Biol. and Med.*, 56: 173, 1944.

[19] A. S. Wiener and H. Karowe, *Jour. Immunol.*, 49: 51, 1944.

[20] A. S. Wiener, I. Davidsohn and E. L. Potter, *Jour. Exp. Med.*, in press.

TABLE 6

REACTIONS OF ANTI-O SERA WITH BLOODS OF THE VARIOUS GROUPS

Blood of group	Reactions with antisera				Reaction with anti-O serum
	anti-A	anti-A_1	anti-B	Genotype	
O	Neg.	Neg.	Neg.	OO	Strong
A_1	Pos.	Pos.	Neg.	A_1A_1	Neg.
				A_1A_2	Weak
				A_1O	
A_2	Pos.	Neg.	Neg.	A_2A_2	Strong
				A_2O	
B	Neg.	Neg.	Pos.	BB	Neg.
				BO	Weak
A_1B	Pos.	Pos.	Pos.	A_1B	Neg.
A_2B	Pos.	Neg.	Pos.	A_2B	Weak

was caused by the fact that anti-O sera, like anti-Hr sera, are usually of low potency, so that consistent positive reactions were obtained only with bloods of groups O and A_2. Wtih more potent anti-O sera, the reactions obtained agree closely with the predictions under the theory proposed above.

BROOKLYN, N. Y. ALEXANDER S. WIENER

ANTIBACTERIAL SUBSTANCES IN ORGANS OF HIGHER PLANTS

THE presence in higher plants of substances with antibacterial properties has been reported in previous publications.[1, 2, 3, 4, 5, 6, 7] The work of Fleming, Florey, Waksman and many others has shown that such substances present in lower plants have important biological significance. Hence, a more intensive effort in investigating the vast field offered by higher plants seemed to be warranted. The authors have for the past six months been engaged in a systematic review of members of families of higher plants with the aim of discovering and isolating substances with antibacterial properties. Osborn's[8] work in the same field was not known to the authors when this search was begun, hence some duplications occurred.

The hypothetical foundation of this search was twofold. (1) It was known that in the rizosphere of higher plants the growing roots regularly survive the actions of innumerable micro-organisms capable of destroying them. It was concluded that a mechanism must be present in the plants enabling them to counteract potentially destructive microorganisms. One such mechanism is undoubtedly manifested in the secretion of acids within the rizosphere. Other protective mechanisms in plants might be based on antibiotic substances of a specific nature. (2) For centuries plant drugs have been used in all parts of the

[1] E. Glaser and F. Prinz, *Fermentforsch.*, 9: 64, 1926.

[2] O. Stickl, *Zeits. Hyg. Infektkr.*, 108: 566, 1928.

[3] F. Boas, *Ber. D. Bot. Ges.*, 52: 126, 1934.

[4] F. Boas and R. Steude, *Biochem. Zeits.*, 279: 417, 1935.

[5] F. Boas, *Ber. D. Bot. Ges.*, 57: (100), 1939.

[6] O. E. Böcker, *Zeits. Hyg. Infektkr.*, 121: 166, 1939.

[7] Other references are given in the paper of Huddleson *et al.*, published in *Jour. Vet. Asn.*, 105: 394, 1944.

[8] E. M. Osborn, *Brit. Jour. Exp. Path.*, 24: 227, 1943.

world as folk remedies. While some drugs have been accepted for medicinal purposes, most of them have still remained in disregard and their employment has often been relegated into the field of superstition. It was thought that some of these plants might contain principles adverse to the development of undesirable microorganisms in the human body.

The search was, therefore, undertaken with particular consideration (1) of the root system of plants, and (2) of plants mentioned in the folklore of numerous countries as beneficial in their application in cases of bacterial infections.

EXPERIMENTAL

Method. The activity of plant extracts and of their concentrates was tested by a method similar to the one described by Sherwood *et al.*,[9] which is a modifi- by British workers[10] in connection with penicillin research. Sterile filter paper discs (Schleicher and Schuell No. 470) of 12.8 mm diameter were used as carriers of the solutions to be tested. The results were evaluated in a qualitative way by arranging them in groups according to the diameters of zones of inhibition.

Procedure. The plant samples were extracted in a Waring Blendor with four times their weight of distilled water. The extracts were strained through cotton cloth, filter paper discs were dipped into the filtrate and placed on the agar of prepared Petri dishes. In most instances, four test organisms were used: *Staphylococcus aureus, Escherichia coli, Phytomonas phaseoli* and *Phytomonas campestris.* The first two organisms were incubated at 37° for 18 hours; the two plant pathogenes grew at room temperature for 48 hours. After these periods any zones of inhibition were measured.

RESULTS

The search of which this report gives a preliminary account has shown that some higher plants contain antibacterial principles at certain stages of their development. These principles vary greatly as to their potency and distribution within the plants. However, regularity of occurrence under identical conditions was established in most of the plants studied. Thus, the leaves of *Onopordon Acanthium,* the Scotch thistle, contain a principle inhibiting the growth of *Staphylococcus aureus.* However, it is only the second year's growth that produces an active extract in appreciable strength. No other thistles examined contained this principle. Other plants exhibiting similar activity in leafy tissues are *Verbascum Thapsus* and *Paeonia officinalis.*

The authors are in accord with Osborn that certain plants tested by others using different procedures do not give a positive response in the plate test. Horseradish, turnips and *Chelidonium majus* were negative in tests made, as were several cabbage varieties. It is believed that the failure of these and of some other plant extracts to respond positively to the plate test is due to the low degree of their diffusibility.

Fruits of certain representatives of the genera *Lonicera* (Fam. *Caprifoliaceae*), *Vaccinium* (Fam. *Ericaceae*), *Ribes* (Fam. *Saxifragaceae*) and *Sorbus* (Fam. *Rosaceae*) are the carriers of active substances.

Some varieties of *Lonicera tatarica,* one of the honeysuckles, have been studied rather extensively, and a potent substance has been discovered which inhibits the growth of *Staphylococcus aureus* and *Escherichia coli.* The inhibition of the gram-positive organism is more pronounced than that of the gram-negative (Principle A in Table 1). In addition, the fruits contain another principle, not active against gram-positive organisms but strongly interfering with the growth of *E. coli* (Principle B in Table 1). Both principles are extractable with water, ethanol and methanol. Principle B can also be extracted with dioxan. Both principles are less soluble in ethyl acetate, nearly insoluble in chloroform and insoluble in ethyl ether, petroleum ether, toluene and carbon tetrachloride. They are heat stable in boiling water for some time; however, boiling for several hours destroys them.

TABLE 1

ACTION OF PLANT EXTRACTS TOWARD BACTERIA. (CONCENTRATIONS ARE COMPARABLE. THE MOST SUITABLE SOLVENT WAS USED IN EACH CASE)

	Paeonia officinalis	*Onopordon Acanthium*	*Vaccinium corymbosum*	*Lonicera tatarica* Principle A	*Lonicera tatarica* Principle B	*Sorbus Americana*
Staph. aureus ..	+	+	..	++	..	+++
E. coli	+	..	+++p	+	++++p	++++
Ph. phaseoli ...	not tested		+++	++++	++++p	++++
Ph. campestris .	not tested		++	++	++++p	+++

Ranges of inhibition: + = < 20 mm diameter; ++ = 20–25 mm diameter; +++ = 26–30 mm diameter; ++++ = > 30 mm diameter; p = partial inhibition.

Some of Osborn's general observations could be confirmed, for example, the similarity of antibacterial actions throughout a genus. However, considerable differences in the potency of the active principles were noted within genera and even species. The active principles found in the scarlet berries of *Lonicera tatarica* were not present in species and varieties with dark red, orange, yellow and purple fruits.

[9] M. B. Sherwood, E. Falco and E. J. DeBeer, SCIENCE, 99: 247, 1944.
cation of the plate assay method recently described

[10] E. P. Abraham, E. Chain, E. M. Fletcher, H. W. Florey, A. D. Gardner, N. G. Heatley and M. A. Jennings, *Lancet,* II: 177, 1941.

In addition to the inhibitory effect of some plant extracts a peculiar phenomenon of disturbed growth and very often of definite stimulation of the test organisms was observed. These phenomena were similar to those described by Abraham *et al.*[10] They appeared as halos of varying sizes surrounding the zones of inhibition. The stimulation was in some cases of extraordinary strength. Boas[3] called attention to the fact that stimulative principles may be present in plant tissues together with inhibitors. A simultaneous action in this sense might explain the observation mentioned. It is also regarded possible that the inhibitor as it penetrates the agar becomes diluted to such a degree that its action reverses.

The results obtained so far indicate that a wide field is opening up for exploration. In all probability, the problems to be encountered will be of a general biological nature rather than being confined to the interrelations between bacteria and higher plants. Broader aspects are coming into the picture, heretofore me. touched but not yet developed.[1, 3, 5]

The authors envisage the applicability of some of the findings to plant pathological problems, particularly in connection with the treatment of seed-borne diseases not yet controllable. An indication of the effect of an antibiotic on plant pathogenes is given in the work of Brown and Boyle[11] in which two plant pathogenes, *Erwinia carnegieana* and *Corynebacterium sepedonicum*, are shown to be inhibited by penicillin. In the light of the work of Link and Walker[12] it is not illogical to suspect that the resistance of some plants to disease is due to the presence in the host cells of distinct chemical substances which are antibiotic to specific pathogenes. The development of antifungal principles, similar in their action to the antibacterial substances, is not outside the realm of possibility.

E. H. LUCAS
R. W. LEWIS
MICHIGAN STATE COLLEGE OF AGRICULTURE AND APPLIED SCIENCE

SCIENTIFIC APPARATUS AND LABORATORY METHODS

A NEW PROCEDURE FOR THE BIOASSAY OF VITAMIN C[1]

THE basis of an acceptable bioassay procedure for the estimation of vitamin C in foods is a test diet which is devoid of vitamin C but otherwise adequate for the growth and development of the guinea pig. Commonly used diets amply fortified with ascorbic acid have been shown in this laboratory to be nutritionally incomplete for normal growth and reproduction of these animals.

As a result of studies over the past four years involving some 2,000 guinea pigs, a ration mixture has been devised which appears to give promise in vitamin C bioassays. It is vitamin C—free; is palatable enough to be readily eaten; supports normal reproduction of mature females and practically normal growth of the young to maturity and subsequent reproduction; and consists of ingredients of relatively low nutritional variability, thus permitting reproducible results in growth or tooth development. (Normal performance was taken as that obtained on a mixture similar to the one herein reported plus green feed fed ad libitum.)

The feed mixture consists of:

15.0 per cent.	Ground No. 1 feed oats
10.5 " "	Ground No. 5 Canadian northern wheat
25.0 " "	Dried beet pulp
10.0 " "	Linseed oilmeal
15.0 " "	Dried skimmilk
5.0 " "	Non-oily fish meal
5.0 " "	Wheat germ meal
10.0 " "	Dried brewers yeast
4.0 " "	Bone char
0.5 " "	Salt (iodized at 0.1 per cent. KI)

This mixture for feeding is pressed into pellets of about 1/16 inch diameter and 1/4 inch length. In addition to these pellets, guinea pigs are fed every second day by direct administration 0.5 cc of a feeding fish oil to supply vitamins A and D. On alternate days they are given 6 mg alpha tocopherol. These quantities are doubtless in excess of the unknown minimum requirements. Adequate ascorbic acid (not less than 2 mg/day for growing pigs) must of course also be supplied. The significance of the proportions of the diet mixture ingredients is unknown. Doubtless considerable change in the quantities of most of the foods may be made, and some may probably be omitted or replaced with others. The reduction of this formula to one consisting of purified materials is the object of studies now under way at this station.

Using this diet the eight-weeks growth response of young male guinea pigs to graded doses between 0.5 mg and 2.0 mg of ascorbic acid bears a linear relation to the log log of the dose. Female pigs have been found unsatisfactory in growth assays because of higher variability and slower growth rates. The variability in growth response in the male pigs on identical dose levels of the order of 29 per cent. and with 16 pigs per group it required 40 to 45 grams differ-

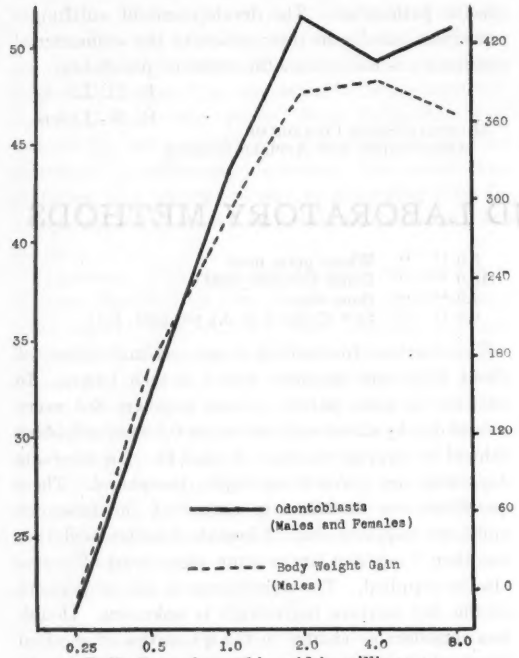
[1] Contribution from the Faculty of Agriculture, McGill University, Macdonald College, Que., Canada. Journal Series No. 197.

[11] J. G. Brown and A. M. Boyle, *Phytopathology*, 43: 760, 1944.

[12] K. P. Link and J. C. Walker, *Jour. Biol. Chem.*, 100: 379, 1933.

ence in mean gain between adjacent dose levels to be statistically significant with a probability of 5 per cent.

In the course of these studies it was discovered that the maximum height (or length) to which the odontoblast cells of the incisor teeth would develop in a given length of assay was related to the dose level of vitamin C. In this procedure the size of the odontoblasts is measured in microns by microscopic examination of sections of decalcified teeth cut longitudinally through the pulp cavity in such a way as to expose the plane from the dental papilla to the crown of the tooth containing the most fully developed odontoblast cells.



Daily dose of ascorbic acid in milligrams.
Left ordinate = microns: right ordinate = grams.

FIG. 1

When such readings were plotted against log dose of ascorbic acid, the relationship was linear between intakes of 0.5 mg and 2.0 mg ascorbic acid. No difference was found between males and females in this characteristic. Replicate tests have given the same relative results though average cell development may differ in different trials. Readings are reproducible by different technicians working independently.

Most important of all is the fact that the variability between animals treated alike is relatively low. In our eight-weeks tests the coefficient of variation in odontoblast development was 12 per cent. as compared to 29 per cent. in the case of live weight gains. The effect on numbers of animals required per treatment which this reduction in variability has is considerable. To obtain a significant mean difference of 10 per cent. between groups would require 10 animals per group in the case of the odontoblast assay as against 65 animals were growth the criterion.

It is noteworthy that the levels of vitamin C between which response by either method bears a relationship to dose are the same. The upper level (2 mg) agrees with that for maximum bone healing reported by Bourne.[2]

In our experience no macroscopic scurvy is found up to eight-weeks duration of assay in young pigs where the daily vitamin C intake has been 0.5 mgms or greater. We have taken this as the minimum level of ascorbic acid suitable for bioassay, on the premise that guinea pigs that are deficient in ascorbic acid to the extent of producing visible lesions can not be depended upon to show either predictable nor reproducible development in the characteristic being used as the criterion of vitamin C intake.

Fig. 1 shows the response by guinea pigs to ascorbic acid as measured (1) by growth and (2) by odontoblast development. For these particular tests the linear relationships were:

For growth : $y = 296.9 + 818.72\ x$, when $x = \log$ log dose.

For odontoblast: $y = 8.0 + 34.09\ x$, when $x = \log$ dose.

Tests are still in progress to determine the minimum length of assay period permissible. Thus far it appears that at least a six weeks feeding period should be used. Assays on three- and four-week periods have not given linear response between dose level and cell development.

E. W. CRAMPTON
BARBARA C. COLLIER
L. D. WOOLSEY
FLORENCE A. FARMER

NUTRITION LABORATORY,
MACDONALD COLLEGE,
PROVINCE OF QUEBEC, CANADA

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SCIENCE NEWS

Science Service, Washington, D. C.

THE CONTROL OF MALARIA

DDT may solve the problem of malaria control in rural areas of the South, it appears from a test conducted by the U. S. Public Health Service in Arkansas. Results of the test, called "striking," were reported by Dr. F. L. Knowles, senior bacteriologist of the office of malaria investigation, U. S. Public Health Service, at the meeting in New York of the American Association of Economic Entomologists.

A widespread federal campaign, to combat the threat of malarial flare-ups resulting from the return of service men who have contracted malaria overseas, is expected to get under way as soon as sufficient DDT becomes available.

DDT supplies "will remain very tight through March and possibly April," John A. R. Rodda, in charge of insecticide allocations in the War Production Board, told the entomologists. "We are still working on military needs, which are consuming practically the entire production. Besides, the raw materials for manufacturing DDT have become critical and are granted only because of the military needs for DDT."

Describing the Arkansas DDT tryout in malaria control, Dr. Knowles pointed out that malaria is an unsolved problem in the southern states because regular control methods are too expensive.

"Spraying the insides of the houses is more effective. The unique residual toxicity of DDT should make it still less expensive and more practical.

"We picked 36 square miles in Arkansas near Helena. This is cotton country. Ninety-five per cent. of the houses are of tenant or share-cropper type, shotgun-construction, newspaper-lined, inhabited by Negroes making only a marginal living. With two high-school boys we sprayed the insides of these last summer, leaving every twenty-fifth house unsprayed as a check.

"Daily inspections of the sprayed houses throughout two months after spraying showed that for that long a period, there was a 94 per cent. average reduction in the number of mosquitoes, resting, alive, on the indoor walls." What happened, he said, was that the mosquitoes came indoors at night, alighted on walls and ceilings bearing an invisible residue of DDT, and were fatally poisoned. This effect takes several hours, but is rapid enough so that "there was an average 80 per cent. reduction in number of living, resting mosquitoes from early morning to afternoon." This technique, it was added, hits the mosquitoes at the strategic time: the night, when they are lying in wait indoors to bite sleeping victims.

The job used an average of .82 of a gallon per house of five per cent. DDT solution. Per house it consumed 10 minutes, took .73 of a man-hour, and cost 74 cents for material and labor.

ITEMS

ACCORDING to statistics of the Metropolitan Life Insurance Company, men and women born in foreign countries, who in the past reared large families in America, now have about the same number of children as native Americans. People who migrated to this country a generation or more ago gave birth, on the average, to 150 children for every 100 born to native parents. In 1940, however, foreign-born women had only about 99 children to every 101 born to native women. The decline in birth rates from 1920 to 1940 was, therefore, greater for the foreign born. For mothers in the twenties, the rate for native Americans fell by about one sixth during these twenty years, while the rate for the foreign-born fell by two fifths. One fact that must be taken into account in interpreting these figures is that the foreign-born dwell predominantly in urban areas, which have always been characterized by relatively low birth rates, while the native-born are more evenly distributed among cities and rural districts.

PRODUCER gas for motor vehicles may be extensively used in Canada during the remainder of the gasoline shortage period, if findings resulting from investigations of substitute fuels made in a report which has just been issued of the Canadian National Research Council are followed. Other promising substitutes studied by the council and found reasonably satisfactory are alcohol and methane or propane. A report by the council has been issued. Wood, wood waste and charcoal were studied by the committee. A variety of portable generators were tested, including eight made in Canada, three from England and two from Sweden. Eleven of these were charcoal equipment, the other two use wood. Two of the thirteen seem to give more satisfactory performance than the others and a considerable number of these two models will be given road tests on cars and trucks. The two given preference burn charcoal, a commodity that may be made available in Canada in sufficient quantities to meet all needs. The first is the cross-draft, dry-blast type, with a single water-cooled copper tuyere or pipe, and no grate. The second is a down-draft, dry-blast type with rotary shaking grates.

THE use of air-cooled steam condensers on mobile electric power plants where water cooling is impossible was described at the same meeting by R. A. Bowman, of the Westinghouse Electric and Manufacturing Company. In connection with the rehabilitation of wartorn areas of the world, he said, there is need for power plants that can be moved easily from one locality to another and put in operation in a short period of time. In some places where they will have to operate water for cooling will not be available. To meet this condition a number of power trains have been built to use air as a cooling medium rather than water. "Tests on the air-cooled condenser for the power train indicate that such a condenser is entirely practical. Because of the poor heat transfer properties and the low specific heat of air, such a condenser in general requires higher auxiliary power, greater investment and higher back pressure on the turbine than would the usual water-cooled condenser." For these reasons its use will probably be confined to places where water is not available.

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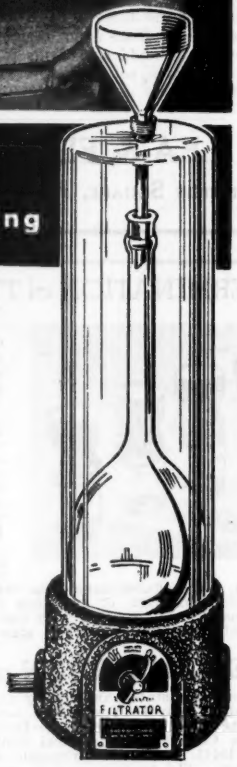

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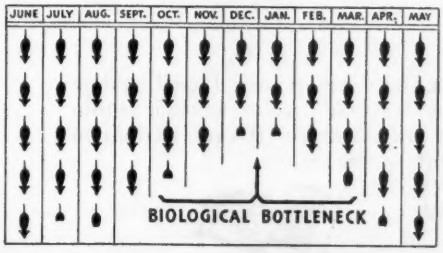

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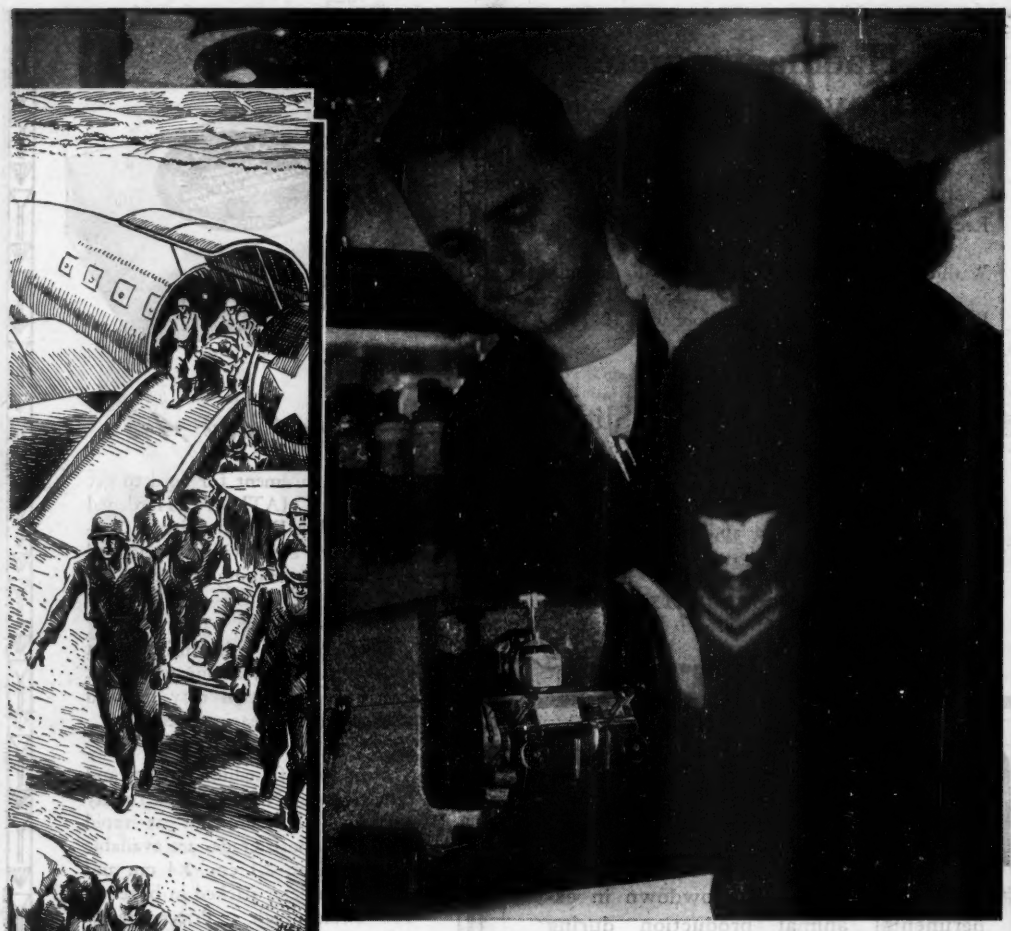

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